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INTRAVENOUS HIPPURIC ACID TEST OF HEPATIC FUNCTION IN INFECTIOUS DISEASES OF CHILDREN

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It has been shown by several authors that of the tests of hepatic function one of the most reliable is the so-called hippuric acid test, introduced by Quick [1] in 1933. This test is based on the response of the liver to benzoic acid administered as sodium benzoate. When sodium benzoate is either ingested or injected intravenously, the benzoic acid radical is conjugated with aminoacetic acid in the liver to form hippuric acid, which is excreted through the kidneys.

The literature concerning the synthesis of hippuric acid has been reviewed elsewhere,[2] and further review will not be attempted here.

From a practical clinical viewpoint it may be assumed that most of the hippuric acid is formed in the liver, although, as is well known, the synthesis of hippuric acid occurs in dogs even after the removal of the liver.[3]

We did not study the renal function in our patients. According to Snapper and Grünbaum [4] and Probstein and Londe,[5] only in the presence of severe impairment of renal function associated with retention of urea may the excretion of hippuric acid be affected. Other authors, on the other hand, deemed it highly important to study the functioning of the kidneys when dealing with the hippuric acid test. Thus Moser and associates [6] concluded that it is of great importance to have an idea of the functional capacity of the kidney before interpreting the results of a hippuric acid test.[7]

The first technic proposed by Quick—in which benzoic acid (as sodium benzoate) is administered by mouth—has been used successfully.

In 1938 Quick [8] proposed as a modification of his earlier ingestion method the test made with intravenous injection of benzoic acid. Since this method is

* Chilean Scholar of the American Academy of Pediatrics.

1. Quick, A. J.: Am. J. M. Sc. **185**:130, 1933.
2. Yardumian, K., and Rosenthal, P. J.: J. Lab. & Clin. Med. **22**:1046, 1937.
3. Mann, F. C.: Medicine **6**:419, 1927.
4. Snapper, J., and Grünbaum, A.: Klin. Wchnschr. **3**:101, 1924.
5. Probstein, J. G., and Londe, S.: Ann. Surg. **111**:230, 1940.
6. Moser, R. H.; Rosemak, B. D., and Hasterlik, R. J.: Am. J. Digest. Dis. & Nutrition **9**:183, 1942.
7. When this paper was ready for publication the article by Machella, Helm and Chornock (J. Clin. Investigation **11**:763, 1942) appeared, in which the authors stressed the close relationship between volume of urine and amount of hippuric acid eliminated. From this paper it would appear that in the future special attention should be given to the urinary volume if one is to interpret correctly the value of the hippuric acid test.
8. Quick, A. J.; Ottenstein, H. N., and Weltcheck, H.: Proc. Soc. Exper. Biol. & Med. **38**:77, 1938.

just as accurate as the earlier one and has the advantage of requiring only one urinalysis, it was deemed more satisfactory for use with children. Besides, it has been pointed out by Londe and Probstein [9] that nausea and vomiting follow oral administration of sodium benzoate and are common and particularly pronounced in children. This is, of course, especially true when a child has an infectious disease. There is, therefore, a further advantage to be gained by intravenous introduction of the chemical.

To date we have found only three studies [10] of the hippuric acid test of hepatic function on children, none of them dealing with the modified method based on intravenous injection, and we have been unable to find any report of the clinical use of the test for children with infectious diseases. Therefore it seems that the results of the application of this test in 128 cases of infectious diseases will be of interest.

EXPERIMENTAL PROCEDURE

The method followed by us is that proposed by Quick,[11] with the only exception that we injected 2 Gm. of sodium benzoate dissolved in 20 cc. of water instead of 1.77 Gm. in the same amount of water. As Quick pointed out, this little difference in the amount of sodium benzoate is without importance. The procedure, then, was as follows: The test was done in the morning, breakfast being omitted. The solution containing 2 Gm. of sodium benzoate in 20 cc. of distilled water was given intravenously at a very slow rate, so that the entire injection took approximately ten minutes. The patient voided before the test, and the urine was collected exactly one hour after the completion of the injection.

The urine was measured, and solid ammonium sulfate was added in the proportion of 5 Gm. for every 10 cc. of urine. When the salt was dissolved, the urine was filtered. Then concentrated hydrochloric acid was added to make the urine distinctly acid to congo red, the acidity being checked with indicator paper. The solution was stirred until the precipitation of hippuric acid was complete. After thirty minutes the crystalline product was filtered, washed with a small amount of cold water and dried. By use of a filter paper on a filter plate, the hippuric acid was weighed without removing the filter paper. To the weight of the hippuric acid was added the quantity remaining in solution. (Approximately 0.1 Gm. of hippuric acid will remain dissolved in 100 cc. of urine containing 50 Gm. of ammonium sulfate.) Following Quick's [11] suggestion, we did not convert the hippuric acid to benzoic acid, as has been the custom with the oral test. Therefore our results are expressed in grams of hippuric acid eliminated in the urine. With this technic, Quick regarded 1 Gm. of hippuric acid as the normal excretion.

The majority of the children whom we tested were most cooperative, and only 6 per cent of them had to be catheterized. No untoward results were obtained, perhaps because of the slow rate of injection—it taking approximately ten minutes to administer the entire dose.

RESULTS

As table 1 shows, in the 16 normal subjects on whom the test was performed the maximum elimination of hippuric acid was found to be 1.65 Gm. and the minimum was 0.90 Gm. We have therefore taken the latter figure as the lower limit of normal and have regarded as pathologic an output of hippuric acid below 0.90 Gm.

Table 2 shows the hippuric acid content, expressed in grams, of the urine of each normal child examined. It will be noted that only one value can be regarded as extremely high. The average normal amount of hippuric acid synthesized by the body from 1.5 Gm. of benzoic acid is about 1 Gm. during the first hour. It seems possible that substances other than hippuric acid may at times be precipi-

9. Londe, S., and Probstein, J. G.: J. Pediat. **18**:317, 1941.

10. (*a*) Bolletino, A.: Lattante **9**:319, 1938. (*b*) Bonduel, A. A.: Día méd. **11**:484, 1939. (*c*) Londe and Probstein.[9]

11. Quick, A. J.: Am. J. Digest. Dis. & Nutrition **6**:716, 1939.

tated under the conditions of this test. Thus, Moser and associates [6] have recently pointed out that in their series of tests 3 patients excreted between 2 and 3.5 Gm., as measured by the precipitation method. Their microscopic examination revealed, besides typical crystals of hippuric acid, other crystals which resembled benzoic acid.

The ages of our patients as well as those of the control subjects ranged from 5 to 11 years, since most of the infectious diseases we have studied have a predilection for these ages.

TABLE 1.—*Intravenous Hippuric Acid Test on Normal Children*

Number of subjects	16
Range of age	5 to 11 years inclusive
Average amount of hippuric acid synthesized	1.11 Gm. (0.90-1.65)

TABLE 2.—*Intravenous Hippuric Acid Test on 16 Normal Children*

Age, Years	Hippuric Acid, Gm.	Age, Years	Hippuric Acid, Gm.
5	0.90	7	1.07
7	0.93	8	1.09
7	0.97	11	1.12
9	0.97	5	1.20
6	0.98	6	1.22
8	0.99	11	1.24
7	1.03	5	1.34
10	1.03	11	1.65

TABLE 3.—*Intravenous Hippuric Acid Test on Children with Infectious Diseases*

Disease	Number of Subjects	Number of Tests
Whooping cough	25	56
Typhoid	33	69
Scarlet fever	22	59
Lobar pneumonia	6	13
Diphtheria	12	29
Typhus	7	15
Acute infections of the upper respiratory tract	10	16
Tuberculosis	8	20
Tuberculous meningitis	5	6
Total	128	283

Table 3 shows the diseases studied, the number of patients and the number of tests performed. The diagnoses were made by both clinical and laboratory means. As is shown in the tables, at least two tests were performed on each of the patients, and on some of them three or four. The length of time between tests depended on the type of disease. Details of the diseases are shown in tables 4 to 11. From these tables we have constructed charts which show clearly the abnormal elimination of hippuric acid. These charts may be analyzed as follows:

Scarlet Fever (chart 1).—Of the 22 patients tested, 82 per cent were found to have functional disturbance of the liver. As the chart shows, the lowest elimination of hippuric acid occurs during the first five days. After the eleventh day

recovery of the liver, as shown by this test, is rapid, provided there are no complications, and by the twentieth day the liver has reached its normal capacity to synthesize hippuric acid in children with a mild form of the disease.

In subjects with moderately severe scarlet fever the recovery of the liver is usually less rapid, taking as long as thirty days in 3 of the children. On these 3

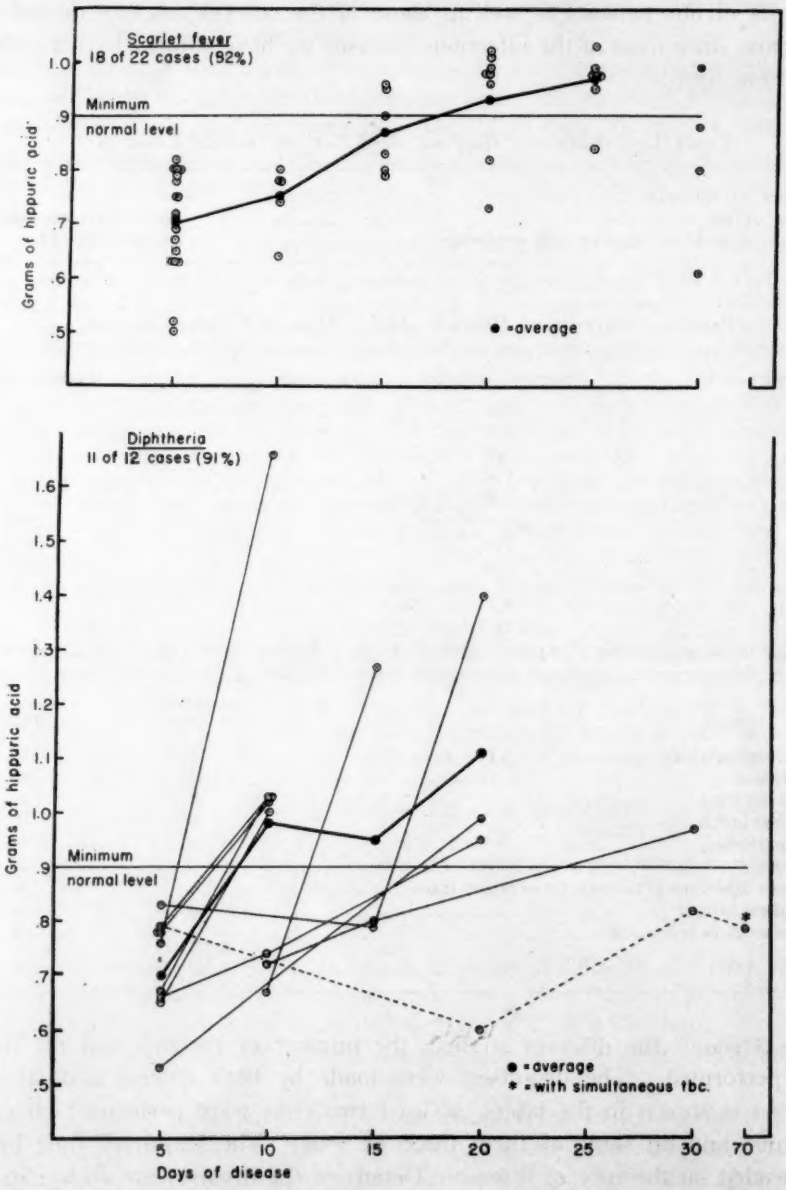

Chart 1.—Abnormal excretion of hippuric acid by children with scarlet fever and diphtheria.

subjects, however, the last tests were performed after the patients appeared to be completely recovered.

These results show that the detoxifying function of the liver is commonly impaired during the early stages of scarlet fever.

In 1940 one of us [12] studied the response of the liver in children by means of the rose bengal test. From this study it was apparent that the liver is damaged in approximately 90 per cent of the children with scarlet fever studied.

Herlitz [13] found that in scarlet fever the bilirubin content of the serum is raised, particularly during the first week of illness, in the acute febrile stage. He studied 31 subjects, of whom 18 exhibited an increase in bilirubin content.

Carslaw,[14] in Great Britain, studied 219 patients with scarlet fever from the viewpoint of hepatic insufficiency by means of an original test. He stated the belief that his results were indicative of impairment of hepatic function and that it might be possible to correlate these results with the development of nephritis. Van Creveld,[15] studying the hepatic function with regard to carbohydrate metabolism, found deviations from the normal in scarlet fever. His results showed that

TABLE 4.—*Intravenous Hippuric Acid Test on Children with Scarlet Fever*

Subject	Age, Yr.	Grams of Acid Synthesized on Day of Disease					Observations
		0-5	6-10	11-15	16-20	21-25	
1	10	0.75	....	....	0.82	0.88	Moderate severity; complicated with suppurative otitis media
2	11	1.02	1.16	....	....	....	Mild
3	10	0.69	....	....	0.73	0.84	Moderate severity
4	9	0.97	....	....	....	0.99	Mild
5	7	0.63	0.64	....	....	....	Moderate severity; discharged from hospital at family's request
6	10	1.04	....	....	0.99	....	Moderate severity
7	9	0.80	....	....	0.98	....	Mild
8	8	0.80	....	0.96	1.02	....	Mild
9	9	0.65	0.80	....	0.98	....	Moderate severity
10	9	0.72	....	0.90	0.99	....	Mild
11	6	0.80	....	....	0.96	....	Mild
12	9	0.78	....	....	1.01	....	Mild
13	12	0.98	....	1.01	....	....	Mild
14	7	0.75	....	0.83	....	0.99	Mild; complicated with otitis media and chorea
15	8	0.52	....	....	....	0.62	Moderate severity; complicated with otitis media and mastoidtis
16	5	0.50	....	0.79	....	0.98	Moderate severity; complicated with otitis media
17	9	0.71	....	0.80	....	1.03	Scarlet fever following an operation
18	10	0.63	0.78	....	....	0.95	Mild
19	9	0.82	....	....	....	0.98	Mild
20	11	0.67	0.78	....	....	0.98	Mild
21	6	0.63	0.74	....	....	0.80	Moderate severity
22	6	0.79	....	0.95	....	0.99	Mild

carbohydrate metabolism is more affected in the fourth to the sixth week of illness. A study by means of the Quick test indicated clearly a lowering of the hippuric acid content of the urine in most of the subjects studied.

The exact mechanism by which scarlet fever impairs the liver is not known; however, it seems plausible that the damage is caused by streptococci and their by-products. It is perhaps of interest that Herlitz [13] expressed the opinion that streptococci have a definite role in the damaging of the liver. The results of the aforementioned author relating to the biliary function of the liver, combined with our results from the hippuric acid and the rose bengal test, lead to the conclusion that the liver in scarlet fever is altered in several of its functions. The results of

12. Meneghello, R. J., and Rossel, P. L.: Rev. chilena de pediat. **11**:507, 1940.
13. Herlitz, C. M.: Acta pædiat. **12**:1, 1931.
14. Carslaw, R. W.: Brit. M. J. **2**:278, 1939.
15. van Creveld, S.: Function of Liver in Scarlet Fever, Am. J. Dis. Child. **44**:265 (Aug.) 1932.

tests by van Creveld [15] suggest that carbohydrate metabolism is also impaired under these conditions.

We were able to characterize the condition of most of our patients with scarlet fever as "mild" or "moderately severe." These patients were not treated with serum or sulfanilamide except in cases in which complications appeared, and in these treatment with sulfanilamide was instituted when the complications first arose.

Diphtheria (chart 1).—Of the 12 subjects studied 90 per cent showed disturbance of hepatic function. For all the 12 patients antitoxic serotherapy was used as soon as the illness was diagnosed, and as a general rule the first test was performed one day after the administration of serum. Nearly all the patients received the serum at the very beginning of the disease.

The first determination almost invariably showed elimination of hippuric acid below 0.8 Gm., but recovery of hepatic function occurred rapidly in all patients except the following: (1) a patient with laryngeal diphtheria; (2) a patient with diphtheria complicated by acute tonsillitis; (3) a child with very severe diphtheria;

TABLE 5.—*Intravenous Hippuric Acid Test on Children with Diphtheria*

Subject	Age, Yr.	Grams of Acid Synthesized on Day of Disease					Observations
		5	10	15	20	30	
81	8	0.53	....	....	0.99	....	Moderate severity
82	4	0.65	1.00	....	....	....	Moderate severity
83	8	0.66	0.74	....	0.95	....	Severe
84	10	0.67	1.03	....	....	....	Mild
85	12	0.76	1.66	....	....	....	Mild
86	9	0.78	1.02	....	....	...	Mild
87	7	0.78	1.03	....	....	....	Mild
88	4	0.79	....	....	0.60	0.82	Diphtheritic laryngitis
						0.78	Primary tuberculosis
89	9	0.83	....	0.78	1.40	....	Mild; complicated with acute suppurative tonsillitis before second determination
90	13	1.37	1.20	....	....	....	Mild
91	5	....	0.67	1.27	....	....	Mild (late administration of serum)
92	6	....	0.72	0.80	....	0.97	Mild (late administration of serum)

(4) a child who received late serotherapy, and (5) a patient in whom recovery was not attained during the entire course of the illness. The data for this child are represented on the chart by a dotted line. He had severe laryngeal diphtheria with primary tuberculosis. He did not enter the hospital until three days after the onset of laryngitis; therefore, his condition was probably rendered even more severe by failure to give serum early. The results are in accord with the pathogenesis of this disease—eminently toxic. The alteration of the parenchyma is, therefore, a function of the potency of the toxin and the speed with which it reaches the cells. It is not surprising, then, that when the serum was administered soon enough to neutralize the toxin as it appeared a minimum abnormal response to our test and rapid recovery were obtained.

Typhoid.—Of the 33 subjects studied, the 9 who showed functional disturbance of the liver were those in whom the disease was moderately severe. It is interesting to note, as chart 2 shows, that recovery of hepatic function is rapid and that in most instances normal elimination of hippuric acid was reached while the patient's temperature was still elevated. It may be noted also that in 1 of these children the typhoid was complicated by whooping cough, in 2 others by bilateral otitis media and in 1 by bronchopneumonia.

In chart 2 are included results for 1 child with mild typhoid which was complicated by scarlet fever during its course. The development of scarlet fever was accompanied with an abrupt reduction in the excretion of hippuric acid from 1.11 to 0.63 Gm.

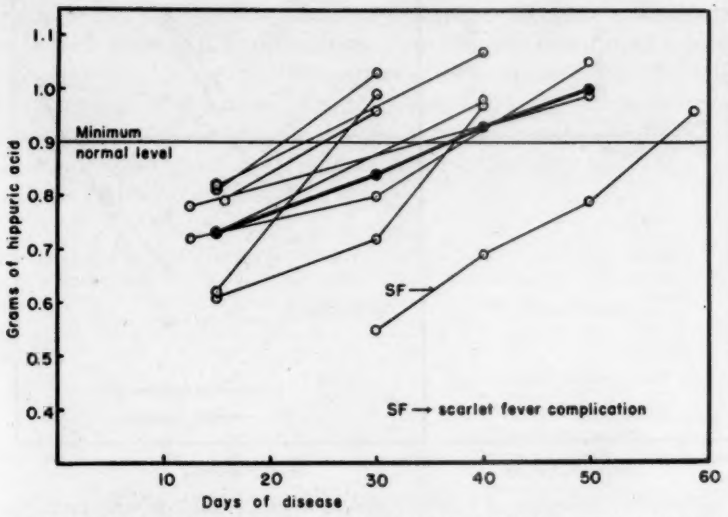

Chart 2.—Abnormal excretion of hippuric acid by 9 of 33 children with typhoid (27 per cent).

TABLE 6.—*Intravenous Hippuric Acid Test on Children with Typhoid*

Subject	Age, Yr.	Grams of Acid Synthesized on Day of Disease						Observations
		0-10	11-20	21-30	31-40	41-50	51	
23	8	0.99	....	....	1.03	....	....	Mild
24	9	1.01	....	1.02	....	....	....	Mild
25	7	1.02	....	....	1.14	....	....	Mild
26	11	1.02	....	1.11	....	....	....	Mild
27	12	1.02	0.98	....	....	....	....	Mild
28	11	1.03	....	1.09	....	....	....	Mild
29	6	1.05	1.06	....	....	....	....	Mild
30	8	....	0.61	0.72	0.97	....	....	Severe; complicated with suppurative otitis media
31	8	....	0.62	0.99	....	....	....	Moderate severity
32	5	....	0.72	0.97	....	1.05	....	Moderate severity
33	10	....	0.73	....	0.98	....	....	Moderate severity
34	8	....	0.78	....	....	0.99	....	Moderate severity; immediately following bronchial pneumonia
35	11	....	0.79	0.96	....	....	....	Moderate severity; complicated with suppurative otitis media
36	6	....	0.81	1.03	....	....	....	Moderate severity; complicated with whooping cough
37	8	....	0.82	....	1.07	....	....	Moderate severity
38	12	....	0.98	1.04	....	....	....	Mild
39	10	....	0.99	....	1.02	....	....	Mild
40	10	....	0.99	....	1.12	....	....	Mild
41	8	....	0.98	1.03	....	....	....	Mild
42	11	....	0.99	1.05	....	....	....	Mild
43	7	....	0.99	....	....	....	....	Mild
44	10	....	1.01	1.09	....	....	....	Mild
45	12	....	1.01	1.02	....	....	....	Mild
46	11	....	1.02	1.09	....	....	....	Mild
47	5	....	1.03	1.05	....	....	....	Mild
48	7	....	1.08	1.09	....	....	....	Mild
49	9	....	1.08	1.10	....	....	....	Mild
50	10	....	1.09	....	....	....	....	Mild
51	9	....	1.11	0.63*	0.77	0.98	....	Mild; complicated with scarlet fever
52	11	....	1.13	....	1.15	....	....	Mild
53	13	....	1.23	....	1.20	....	....	Mild
54	11	....	....	0.55	0.69*	0.79	0.96	Severe; complicated with scarlet fever
55	8	....	....	1.10	....	1.10	....	Mild

* Scarlet fever.

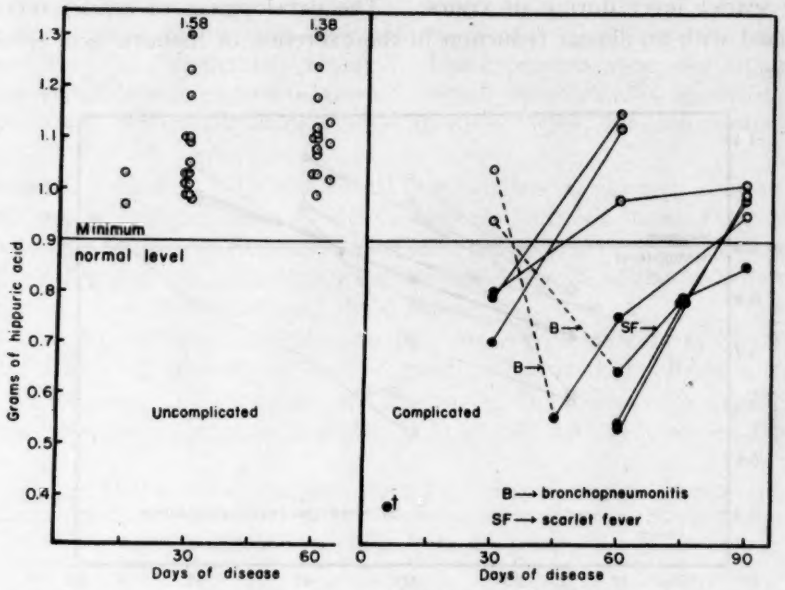

Chart 3.—Abnormal excretion of hippuric acid by 8 of 24 children with complicated whooping cough (33 per cent).

TABLE 7.—*Intravenous Hippuric Acid Test on Children with Whooping Cough*

Subject	Age, Yr.	Grams of Acid Synthesized on Day of Disease: 0-30	31-60	61-90	Observations
56	6	0.38*	....	....	Extremely severe; complicated with bronchial pneumonia and diarrhea
57	7	0.70	1.12	....	Moderate severity; complicated with pleuritis and bilateral otitis media
58	6	0.79	1.15	....	Moderate severity; complicated with bilateral otitis media
59	8	0.80	0.98	1.01	Mild; complicated with suppurative axillar adenitis
60	10	0.94	0.64	0.79† 0.85	Moderate severity; complicated with bronchial pneumonia before the second determination and with scarlet fever before the third determination
61	7	0.97 1.03	....	....	Mild
62	6	0.98	1.03	....	Mild
63	6	0.98	1.18	....	Mild
64	11	0.99	....	1.02	Mild; complicated with pleuritis
65	5	0.99	1.03	....	Mild
66	5	1.01	1.08	....	Mild
67	4	1.01	1.10	....	Mild
68	12	1.03	1.10	....	Mild
69	6	1.04	0.55 0.75	0.95	Extremely severe; complicated with bronchial pneumonia and bilateral otitis media before the second determination
70	8	1.03 1.09	....	....	Mild
71	7	1.05	1.07	....	Mild
72	8	1.10	....	1.09	Mild
73	8	1.10	1.11	....	Mild
74	7	1.18	1.12	....	Mild
75	10	1.23	1.24	....	Mild; complicated with pleuritis
76	8	1.58	1.38	....	Mild
77	6	....	0.53‡	0.78 0.99	Extremely severe; complicated with bronchial pneumonia, pleuritis and tuberculosis
78	5	....	0.54	0.78 0.98	Severe; complicated with bronchial pneumonia
79	7	....	0.99	1.13	Mild
80§	6	0.67†	0.62	....	Mild; preceded by pulmonary tuberculosis

* Died six days after admission.
† Scarlet fever.
‡ Tuberculosis.
§ The data for this subject have been omitted in the charts because tuberculosis accounted for most of the severity of the clinical course.

Whooping Cough (chart 3).—Of the 24 patients studied, only in those who had complications was there functional hepatic disturbance. Therefore, only the results for 8 of the 9 patients with complicated pertussis are represented graphically. Data for the ninth child were excluded because of tuberculosis.

In discussing whooping cough, it is important to call attention to the fact that the number of days of disease as recorded on the chart is somewhat arbitrary, since, as is well known, it is difficult to ascertain the moment at which the disease is first contracted. None of our patients with uncomplicated whooping cough showed impairment of the liver. On the other hand, the subjects who showed low elimination had complications of bronchial pneumonia, suppurative otitis media, pleuritis, or adenitis, which thus suggested the probability that the pyogenic microorganisms were also acting on the liver.

TABLE 8.—*Intravenous Hippuric Acid Test on Children with Pulmonary Tuberculosis*

Subject	Age, Yr.	Results of Tests Performed at Average Intervals of 45 Days				Observations
		Gm.	Gm.	Gm.	Gm.	
116	4	0.79	0.60	0.82	0.78	Primary tuberculosis accompanying diphtheria
117	6	0.67	0.92	....	....	Primary tuberculosis accompanying whooping cough
118	6	0.53	0.78	0.99	....	Primary tuberculosis accompanying whooping cough
119	11	0.68	0.70	0.92	....	Primary tuberculosis accompanying typhus
120	10	0.68	0.88	....	....	Primary tuberculosis
121	11	1.11	1.18	....	....	Primary tuberculosis
122	11	0.70	0.52	....	....	Caseous pneumonia; severe
123	12	0.70	0.80	....	....	Primary tuberculosis accompanying erysipelas

TABLE 9.—*Intravenous Hippuric Acid Test on Children with Lobar Pneumonia*

Subject	Age, Yr.	Grams of Acid Synthesized on Day of Disease					Observations
		2	5	10	15	20	
93	12	0.59	....	1.22	....	....	Mild
94	11	0.62	....	1.06	....	....	Mild
95	9	0.65	....	1.06	....	....	Mild
96	10	0.74	....	0.77	0.82	1.03	Moderate severity
97	8	....	0.73	0.99	....	....	Mild
98	10	....	0.80	1.02	....	....	Mild

Lobar Pneumonia, Typhus, Tuberculous Meningitis, Tuberculosis and Acute Infections of the Upper Respiratory Tract.—Observations on patients with these conditions have been represented only in tabular form, because of the small number of subjects studied. In addition to that, for children with diseases such as tuberculosis it was impossible for us to determine the day of their contracting the disease. Nevertheless, we deem it informative to incorporate these data in tabular form.

Lobar Pneumonia: Table 9 shows that all 6 of the subjects with typical pneumonia had abnormal elimination of hippuric acid at the very beginning of the disease. In fact, all of the subjects had values lower than 0.90 Gm. for daily elimination of hippuric acid before the fifth day of illness. The recovery of hepatic function as shown by the increased elimination of hippuric acid occurred immediately after the crisis except in 1 case (subject 93, table 8), in which normal excretion of hippuric acid was reached one day before the crisis. In another case

(subject 96), with an uncommon course, the pneumonia was complicated with a pleural effusion. Since lobar pneumonia in older children has a good prognosis and a benign course, these patients did not receive any therapy; furthermore, sulfanilamide was not given, to make sure of not adding a toxic effect of the drug.

Acute Infections of the Upper Respiratory Tract: These infections were mild and without complications in our subjects, and disturbance of hepatic function was not detected except in 2 children.

TABLE 10.—*Intravenous Hippuric Acid Test on Children with Acute Infections of the Upper Respiratory Tract*

Subject	Age, Yr.	Grams of Acid Synthesized on Day of Disease			Observations
		5	10	15	
106	4	0.73	1.03	....	Mild
107	8	0.76	....	1.02	Mild
108	11	0.97	1.07	....	Mild
109	8	0.98	....	....	Mild
110	7	1.02	....	....	Mild
111	12	1.02	....	....	Mild
112	9	1.07	....	1.10	Mild
113	12	1.03	1.08	....	Mild
114	8	1.02	1.08	....	Mild
115	11	....	1.01	....	Mild

TABLE 11.—*Intravenous Hippuric Acid Test on Children with Typhus*

Subject	Age, Yr.	Grams of Acid Synthesized on Day of Disease				Observations
		10	20	25	60	
99	11	0.68	0.70	....	0.92	Moderate severity; complicated with pyelonephritis and primary tuberculosis
100	11	0.85	1.10	....	....	Mild
101	7	0.87	1.03	....	....	Mild
102	7	0.96	1.06	....	....	Mild
103	6	0.98	....	1.02	....	Mild
104	7	1.02	....	1.10	....	Mild
105	7	1.07	....	1.07	....	Mild

TABLE 12.—*Intravenous Hippuric Acid Test on Children with Tuberculous Meningitis*

Subject	Age, Yr.	Results, Gm.
124	10	0.39
125	12	0.44
126	6	0.41
127	6	0.41
128	9	0.60
		0.48*

* Test performed one day before death.

Typhus: We have studied 7 subjects with mild typhus, of whom only 1 appeared to have some functional disturbance of the liver. This child also had pyelonephritis and primary tuberculosis.

Tuberculous meningitis: All 5 patients with tuberculous meningitis eliminated almost invariably very low quantities of hippuric acid. These tests were performed during the real meningitic period.

Tuberculosis: As far as tuberculosis is concerned, too few patients with the uncomplicated disease were available to enable us to draw sound conclusions. Nevertheless, it is interesting to note that whenever the disease was complicated

there occurred impairment of hepatic function. We should also like to recall that the patients with tuberculous meningitis gave the lowest figures of any in our study.

SUMMARY

The purpose of this study was to determine abnormalities of hepatic function in children with infectious diseases.

The means used to investigate hepatic function was the standard hippuric acid test, with one important modification—intravenous injection instead of ingestion of the benzoic acid. This modification was made for considerations of greater accuracy, saving of time and diminished toxic effects in dealing with children.

To obtain standard figures for elimination of hippuric acid we performed tests on 16 normal children, the results of which yielded the figure of 0.9 Gm. for minimum hippuric acid content of urine eliminated one hour after the injection of sodium benzoate. We next studied 128 children with 9 infectious diseases.

Briefly summarized, the results are as follows. The liver appeared to be functioning abnormally in 80 per cent of 22 patients with scarlet fever; in 91 per cent of 12 patients with diphtheria; in 27 per cent of 33 patients with typhoid; in 100 per cent of the 6 patients with lobar pneumonia, and in 100 per cent of the 5 patients with tuberculous meningitis. (These patients showed the lowest excretion of all.) The diseases in which hepatic function may roughly be classed as normal were whooping cough, typhus and acute infections of the upper respiratory tract.

Dr. Luis Vargas assisted in this study.

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STUDIES ON CONTROL OF ACUTE INFECTIONS OF RESPIRATORY TRACT

II. ORAL ADMINISTRATION OF SULFADIAZINE AT THE ONSET OF ACUTE RESPIRATORY ILLNESSES

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A preliminary report [1] on the use of sulfadiazine at the onset of acute infections of the respiratory tract in a highly susceptible population described a decrease in the severity and the duration of the disease in many of the cases observed. In some treated patients, however, the course of infection appeared to be unaffected, and in others a secondary rise in temperature occurred shortly after withdrawal of the drug. The study has been continued, and clinical data are now available on the outcome in 162 cases.

The work has been carried out at Letchworth Village, an institution of the state of New York for feebleminded patients,[2] among children with the lowest mental rating and with an unusual degree of susceptibility to acute infections of the respiratory tract and secondary complications.[3] Two methods of choosing subjects for the tests were tried in two different cottages (cottages Y and Iota), each with about 130 children varying in age from 3 to 14 years. In cottage Y, sulfadiazine was used in alternate cases in order of occurrence. In cottage Iota, the inmates were allocated to test groups at the onset of the study, and new entrants were assigned to the control or the treated group in order of admission to the cottage. In each cottage, the outcome was equally favorable to the treated group. The study had to be interrupted in cottage Y, where alternate patients were being treated, because of the tendency to select for drug therapy the more severely infected or more susceptible children when several became ill at about the same time. In cottage Iota, however, this tendency was eliminated by selection of definite test groups before onset, and the study was continued. The present report summarizes the clinical results obtained in this cottage over a twenty week period, from Dec. 14, 1941 to May 2, 1942, when the incidence of colds was high.

Control and treated patients were managed alike in the cottage, except for the giving of sulfadiazine to patients in the treated group. All patients were put to bed at the first recognizable signs of illness and usually given an enema at once. During the acute stage, they were given a light diet and an increased amount of citrus juices. Local applications and acetylsalicylic acid were prescribed as needed.

From the Division of Infectious Diseases, the Public Health Research Institute of the City of New York.

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1. Siegel, M.: Studies on the Control of Acute Respiratory Infections: I. Preliminary Report on the Oral Administration of Sulfadiazine at the Onset of Acute Respiratory Illnesses, J. A. M. A. **119**:783-785 (July 4) 1942.

2. A Survey of Methods of Care, Treatment, and Training of the Feebleminded Made at Letchworth Village, State of New York, Department of Mental Hygiene, State Hospital Press, Utica, N. Y., 1937.

3. Siegel, M., and Muckenfuss, R. S.: A Study in Active Immunization Against Epidemic Influenza and Pneumococcus Pneumonia at Letchworth Village: II. Results of Active Immunization Against Pneumonia with Pneumococcal Polysaccharide, Am. J. Hyg. **34**:70-109 (Nov.) 1941.

Those who became severely ill were sent to the hospital, where they were treated according to their needs, irrespective of their test grouping in the cottage.

The patients in the treated group received sulfadiazine as soon as symptoms of respiratory illness appeared. The initial dose was 0.5 Gm. for those weighing less than 50 pounds (23 Kg.) and having a temperature of less than 102 F.; all others received 1 Gm. The initial dose was followed by 0.5 Gm. every four hours for three doses. After that, 2 Gm. was used daily, divided into four doses of 0.5 Gm. each at 8, 12, 4 and 8 o'clock. The drug was given for at least four days or until the temperature was less than 100 F. for twenty-four hours and all signs of infection had receded. In most cases the blood level of free sulfadiazine [4] varied from 4 to 8 mg. per hundred cubic centimeters during the maintenance period of drug therapy.

RESULTS

The number of inmates affected in each test group and the number of infections of the respiratory tract observed during the twenty week period from Dec. 14, 1941 to May 2, 1942 are shown in table 1. The test groups were comparable with respect to the number of affected inmates and the number of colds per inmate.

TABLE 1.—*Frequency of Observed Infections of the Respiratory Tract*

Number of Infections per Inmate	Number of Subjects		Number of Infections *	
	Treated Group	Control Group	Treated Group	Control Group
0	30	32	0	0
1	17	20	17	20
2	16	9	31 (1)	17 (1)
3	7	7	20 (1)	20 (1)
4	2	4	6 (2)	15 (1)
5 or 6	2	2	8 (3)	8 (2)
Total	74	74	82 (7)	80 (5)

* Numerals in parentheses refer to the number of infections excluded from the study for reasons given in the text.

In all, 162 infections were considered, 82 in patients of the treated group and 80 in patients of the control group.

Excluded from the study were 7 infections in the treated group for which sulfadiazine was not used as had been previously planned, because the diagnosis was doubtful at the onset or the illness was so mild that it was not treated. From infections in patients of the control group, 5 were excluded because of early administration of the sulfonamide compound. The patients required hospitalization at the onset, and treatment could not be properly withheld or delayed, because a pneumonic infection was suspected in each instance. This type of selection tended to remove from the study some infections in the more severely ill children of the control group and some in the less severely ill of the treated group.

The severity and duration of the infections studied varied widely. They affected the nose, throat or chest. The most common symptoms were coryza, sore throat, cough, fever and anorexia. Hemolytic streptococci and many different types of pneumococci were isolated from smears of material from the throat.[5] The most common types of pneumococci found were I, III, XI A (Gorman), XVIII A (Dougherty), XIX and XXII. In about 20 per cent of the cases, no

4. Determined through the courtesy of Dr. Jesse G. M. Bullowa at Harlem Hospital, New York.

5. The typing was done by the Pneumonia Control Division of the Department of Health of the City of New York.

significant organism was obtained in a single smear of material from the nasopharynx.

In the analysis of the clinical data, those for the treated and for the control groups were arranged according to (1) the number of colds per person and (2) the maximum temperature on the first day of illness. In each of these arrangements the following objective data were noted: average duration of fever (temperature of 100 F. or more by rectum) after the first day's treatment in bed; rise in temperature in the early stages of illness following the first day's treatment (primary rise); secondary rise in temperature; number of patients requiring hospitalization.

A summary of the results obtained classified according to the number of colds per person in the control and in the treated patients is shown in table 2. The average duration of fever after the first day's treatment was one and one-tenth days for the treated patients and three and one-tenth days for the controls. These averages represent totals of ninety febrile days for eighty-two infections in treated patients and of two hundred and forty-nine febrile days for 80 infections in the control groups.

TABLE 2.—*Comparison of Results in Treated and in Control Patients with Acute Infection of the Respiratory Tract, Arranged According to the Number of Infections per Patient*

Infections of Respiratory Tract per Person	Number of Persons Affected		Number of Infections *		Temperature Response to Infection of Respiratory Tract: Average Duration of Fever After First Day's Treatment		Infections with Primary Rise in Temperature		Infections with Secondary Rise in Temperature		Infections Requiring Hospitalization	
	Treated	Controls	Treated	Controls	Treated	Controls	Treated	Controls	Treated	Controls	Treated	Controls
1	17	20	17	20	0.9	4.0	0	9	1	5	0	6
2	16	9	31 (1)	17 (1)	1.2	3.3	3	5	6	4	3	3
3 or more	11	13	34 (6)	43 (4)	1.1	2.6	1	4	4	13	1	10
Total	44	42	82 (7)	80 (5)	1.1	3.1	4	18	11	22	4	19

* Numerals in parentheses refer to the number of infections in each test group omitted from the study: infections in the treated group for which sulfadiazine was not used and infections in the control group for which it was.

A primary rise in temperature was observed in 4 infections in patients from the treated group and in 18 in patients from the control group. In the 4 patients treated the temperature rose on the third day of drug therapy. Two patients had lobar pneumonia and required hospitalization, while 2 had acute nasopharyngitis which receded on the fifth day of illness without complications. Of the 2 with lobar pneumonia, 1 was a boy of 8 years weighing 53 pounds (24 Kg.). His temperature rose from 101 to 104 F. on the third day of a respiratory illness, when he was transferred to the hospital. He died on the following day. A limited postmortem examination revealed pneumonia of the lower lobes. He had received 2.5 Gm. of sulfadiazine on the first day of illness, 2 Gm. on the second and 1 Gm. on the third day, shortly before his transfer to the hospital. At this time his blood level of free sulfadiazine was 2.6 mg. per hundred cubic centimeters. In the hospital, 3 Gm. of sulfathiazole was given within twenty-four hours. No significant organisms could be isolated from a single smear of material from the throat on the third day of illness.

The second child in whom lobar pneumonia developed during sulfadiazine therapy was a boy of 5 years weighing 28 pounds (13 Kg.). From 2 to 2.5 Gm. of sulfadiazine was given daily for four days without effect. A rash appeared at

this time, and the use of the drug was discontinued. On the fifth day he was transferred to the hospital, where 2 Gm. of sulfathiazole was given daily for four days. The temperature fell by crisis on the eighth day. A roentgenogram on the fifth day showed evidence of consolidation confined to the upper half of the lower lobe of the left lung. Pneumococci of type XVIII A (Dougherty) were recovered from smears of material from the throat taken on the third and fifth days of illness.

Of the 18 control subjects with a rise in temperature in the early stage of their illness, in 4 pneumonia developed, in 8 acute bronchitis and in 6 acute nasopharyngitis. Eight had to be sent to the hospital. One died there on the sixth day of illness with bronchopneumonia of undetermined cause.

A secondary rise in temperature was observed in 11 infections in treated patients and in 22 in control patients. In the treated patients, the rise occurred from the fourth to the tenth day of illness and one to six days after the withdrawal of sulfadiazine. In each instance the temperature fell within twenty-four to forty-eight hours after reintroduction of the drug and no complications developed. In the patients of the control group, 1 or more secondary rises in temperature occurred from the third to the eighteenth day and lasted from one to nine days. They were related to the development of pneumonia in 2 cases, of acute bronchitis in 8, of otitis media in 2 and of nasopharyngitis or sinusitis in the others.

Hospitalization was required in 4 infections in treated patients and in 19 in controls. In 9 of them the patient had pneumonia, 2 in the treated group (previously mentioned) and 7 in the control. In 14 other infections (2 in treated and 12 in control patients), pneumonia was suspected when the patient was sent into the hospital but the diagnosis was not confirmed and the conditions were considered as either acute bronchitis or nasopharyngitis.

The recurrence of acute infections of the respiratory tract in the same patient permitted a comparison of the relative efficacy of the drug in the first and in succeeding treated attacks. Such comparative data were available for 25 patients with 25 first and 37 subsequent infections. The average duration of fever after the first day's treatment was one and three-tenths days for the first attacks and nine-tenths day for the succeeding attacks. A primary rise in temperature was seen in 3 first infections and in 1 second infection. A secondary rise in temperature occurred after the withdrawal of the drug in 3 first and in 6 subsequent attacks. Hospitalization was required once for a first infection because of lobar pneumonia and three times for a subsequent infection. These differences are not statistically significant.

A summary of the results obtained in the control and in the treated patients arranged according to the maximum temperature on the first day of illness is shown in table 3. The two test groups were evenly matched with regard to the temperature on the first day. Among the control patients with less than 103 F. at the onset, a primary rise in temperature was seen almost six times more frequently than among the treated. Secondary rises in temperature were not uncommon in either group, though less frequent in the treated. In every infection in a treated patient, the secondary rise occurred after withdrawal of the drug. The average duration of fever was consistently two to three times longer in control than in treated patients. The number of infections in which hospitalization was required was from three to six times greater in patients of the control group than in those of the treated group.

The average daily temperature in the control and the treated patients arranged according to maximum temperature on the first day is graphically shown in the chart. The treated patients showed a sharp drop in temperature after the first day of

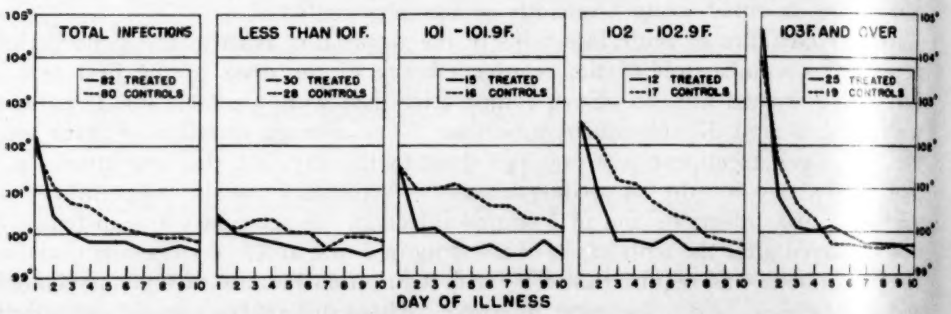
treatment. The average temperatures varied from 100 to 101 F. on the second day, were below 100.5 F. on the third day and were 100 F. or less on the fourth. In the control groups, there was a more gradual drop in temperature; the averages varied between 100 and 102 F. on the second day, between 100 and 101 F. on the third and fourth days and below 101 F. on the fifth. The treated patients in all the groups tended quickly to reach low levels, which were more gradually approached by the controls. The average temperature was below 100 F. for all treated patients on the third day and for all controls on the seventh day.

On the whole, the treated patients did noticeably better than the controls.

TABLE 3.—*Comparison of Results in Treated and in Control Patients with Acute Infection of the Respiratory Tract, Arranged According to the Maximum Temperature on the First Day of the Acute Illness*

Maximum Temperature on First Day	Infections *		Average Duration of Fever After First Day's Treatment		Infections with Primary Rise in Temperature		Infections with Secondary Rise in Temperature		Infections Requiring Hospitalization	
	Treated	Controls	Treated	Controls	Treated	Controls	Treated	Controls	Treated	Controls
100 or less.....	30 (5)	28	0.6	1.9	2	6	4	6	0	2
101.....	15 (1)	16	1.3	4.8	1	8	3	7	1	6
102.....	12	17	1.2	4.1	0	3	2	6	0	2
103 or more.....	25 (1)	19 (5)	1.4	3.0	1	1	2	3	3	9
Total.....	82 (7)	80 (5)	1.1	3.1	4	18	11	22	4	19

* Numerals in parentheses refer to the number of infections in each test group omitted from the study: infections in the treated group for which sulfadiazine was not used and infections in the control group for which it was.



Average daily temperatures in 162 respiratory infections in sulfadiazine-treated and untreated patients arranged according to the patient's maximum temperature on the first day of illness. Maximum temperature on first day of illness is indicated by the figures in the top of each box. In the control patients there were originally 24 infections during which the temperature reached 103 F. or over on the first day of illness. For 5 (20 per cent) of the patients who were more seriously ill chemotherapy was required at the onset and data for them were excluded from the study. The remaining 19 infections were in a selected group of control patients in whom the infections were proportionately less severe and in whom the course approximated that observed in the treated test group.

Irrespective of the type of onset, the progress of infection usually appeared to be checked after the first day's treatment with sulfadiazine. There was usually evidence of regression by the second day, which continued during the course of therapy. About 5 per cent of the infections became worse despite treatment, and of an additional 9 per cent improvement was delayed and appeared to be unrelated to the effects of sulfadiazine. Of the patients whose infections were not modified by sulfadiazine, in 2 lobar pneumonia detectable on the third day of treatment developed; 1 of these children died, and 1 recovered. In 12 per cent of the patients

evidence of infection reappeared shortly after sulfadiazine therapy was discontinued but the symptoms disappeared rapidly after the child was again given the drug. The need for hospitalization arose in 5 per cent of the infections, half of which had been treated for less than twenty-four hours. There were no serious toxic effects from the drug in the dosage used nor evidence of sensitization in this limited experience.

In patients of the control group, the course and severity of the infections varied widely. In many they were mild, and recovery followed promptly. However, in about 22 per cent of the infections evidence of progression early in the disease was shown; in about 28 per cent there was evidence of an exacerbation or complication. The course was entirely unpredictable; neither the temperature at the onset nor the local symptoms were reliable prognostic guides. A few children with extremely high temperatures at the onset were well in two or three days, while others, with little fever and apparently benign physical symptoms on the first day of illness, became seriously sick and remained ill for a long time.

COMMENT

The evidence recorded indicates that the severity of many acute respiratory illnesses observed in the study could be modified by oral use of sulfadiazine early in the course of the disease. The beneficial effects were measurable in terms of reduction in the duration of fever and in the frequency of pneumonia and other severe illnesses requiring hospitalization. Other clinical effects, such as reduction in toxemia and in degree of debility, were also noted. These results are attributable to the inhibitory activity of sulfadiazine on the susceptible bacteria which are active in many acute infections of the respiratory tract. Effective chemotherapy of such infections can be expected to abort or control bacterial invasion before it becomes extensive or has seriously decreased resistance of the host.

Some illnesses were apparently unaffected by early sulfadiazine therapy. These were presumably due to uncomplicated virus infections or to bacterial overgrowth refractory to the action of sulfadiazine under the existing conditions. In the latter instance, bacterial infection progressed despite therapy, as was observed in 2 patients in whom detectable signs of pulmonary consolidation developed on the third day of illness.

In certain patients, there was a secondary rise in temperature shortly after chemotherapy was discontinued. This was interpreted as representing either an exacerbation of the previous infection or the onset of a completely new infection. Such effects are to be expected with premature withdrawal of a bacteriostatic agent like sulfadiazine, particularly in highly susceptible persons characterized by slow recovery and frequent reinfections. Consequently, it becomes necessary to prolong the period of treatment and observation even after return to normal temperature.

In considering the application of the methods used at Letchworth Village to the general population, it should be noted that infection of the respiratory tract is as a rule inordinately common, severe and prolonged among the inmates observed at the institution. Under such conditions, therefore, the use of a bacteriostatic agent, such as sulfadiazine, becomes particularly desirable, whereas administration of this particular drug to the general population would seem to depend on both the subject concerned and the type of infection. Its use should be considered for persons highly susceptible to secondary complications amenable to the action of the drug and for persons with an infection which is more or less commonly complicated by a serious bacterial invasion, such as a severe epidemic form of influenza or of measles. A more generalized application seems inadvisable until more is

known about the undesirable effects of sulfadiazine, such as sensitization to it,[6] the toxic effects of its prolonged or repeated use [7] and the development of strains of organisms resistant to it in vivo.[8]

SUMMARY AND CONCLUSIONS

Clinical data have been presented on the use of sulfadiazine at the onset of acute respiratory illnesses in 82 infections in treated patients and in 80 control patients observed during a twenty week period, from Dec. 14, 1941 to May 2, 1942. The subjects were feebleminded boys highly susceptible to infections of the respiratory tract.

In general, it may be said that the illnesses were milder and of shorter duration in the drug-treated group than in the untreated group. In some infections, however, the disease appeared to be unaffected by the treatment, and in 2 instances lobar pneumonia was detected on the third day of treatment and was the cause of death in 1. In other cases, symptoms reappeared shortly after withdrawal of the drug and were indicative either of undertreatment or of a new infection.

The use of sulfadiazine at the onset of acute infections of the respiratory tract in an effort to modify the severity of the illness and to reduce the frequency of secondary bacterial infections and complications is still in the experimental stage. Its application should be restricted until more data are available on toxicity, sensitivity and strain resistance.

The physicians at Letchworth Village, particularly Dr. Harry C. Storrs, Superintendent, and Dr. Nathaniel Bernstein, aided in this work.

The sulfadiazine was supplied by Lederle Laboratories, Inc., Pearl River, N. Y.

Foot of East Fifteenth Street.

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DELAYED PRODUCTION OF POLIOMYELITIS ANTIBODIES

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It is difficult to understand why neutralizing antibodies against poliomyelitis virus are not always found in the serums of patients immediately after they recover from the acute stage of the disease. In a few instances in my experience they did not appear until a long time after recovery. There has been some parallel experimental evidence in animals, for it has been found that when a horse is inoculated with poliomyelitis virus some time may elapse before antibodies appear. With 2 horses it was found that the first specimens of blood, taken within a few weeks after the end of a series of injections of virus, not only failed to neutralize the virus but actually caused an accelerated production of the disease in Macaca mulatta monkeys.

The poliomyelitis antiserum obtained from 1 horse described previously [1] contained potent antibodies which could neutralize not only homologous (Flexner's M. V.) but several heterologous (Australian, Kramer, Trask's S. K. and Flexner's weak) strains of virus. Recently, Jungeblut reported that a concentrated fraction of this serum completely neutralized his murine SK strain of poliomyelitis virus.[2]

In the previous series of experiments (1935-1936), 3 horses were used. One of these, C, normally possessed neutralizing antibodies in its blood serum. Despite the fact that it was inoculated with both "fortified" and "unfortified" antigens, there was never any increase in antibodies. (An unfortified antigen was a suspension of spinal cord virus, either purified or unpurified, in a solution of sodium chloride; when a paratyphoid-colon bacillus filtrate enteric toxin was used instead of the sodium chloride solution, the antigen was termed "fortified." [1a]) Horse A was inoculated with "fortified" and horse B with "unfortified" antigen. A acquired a higher titer of neutralizing antibodies in its blood serum than did B, but the titer dropped to the level of B's within six months after the last immunizing dose.

EXPERIMENTS

Experiment 1.—Although 2 of 3 horses immunized had shown a lag in the production of neutralizing antibodies for homologous as well as for several heterologous strains of virus, it was not certain whether these results could be

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1. Toomey, J. A.: (*a*) Poliomyelitis Antiserum Obtained from Horses, Am. J. Dis. Child. **53**:1492 (June) 1937; (*b*) II. Neutralizing Effect Against Various Strains of Virus, ibid. **55**:1261 (June) 1938.

2. Jungeblut, C. W.; Sanders, M., and Feiner, R.: Studies in Rodent Poliomyelitis: I. Further Experiments with the Murine Strain of SK Poliomyelitis Virus, J. Exper. Med. **75**:611, 1942; III. Experimental Poliomyelitis in Guinea Pigs Produced with the Murine Strain of SK Poliomyelitis Virus, ibid. **76**:31, 1942.

repeated. It was therefore decided to immunize other horses in like fashion and to repeat the original experiments of 1935. In particular, the answers to two questions were sought: 1. Would the combination of early specimens of serum (obtained a few weeks after the completion of immunization) and virus accelerate the production of poliomyelitis when injected intracerebrally into monkeys? 2. If neutralizing antibodies were not found immediately after immunization, would they be found at some subsequent date, as in my previous experiments?[1]

In the earlier experiments the first two injections were made with suspensions of virus from the cord tissue. All virus material in the present experiments was eluted and purified to avoid the production of any specific antibody response to this brain tissue in the inoculated animal—an antibody which might interfere with the neutralization tests. The test virus was also eluted and purified.

The blood serums of horses D and E were tested on Feb. 27, 1937 and were found to be lacking in neutralizing antibodies.

The procedure was as follows: Each neutralization test for each specimen of horse serum in this and all succeeding experiments required 3 Macaca mulatta monkeys. To 0.2 cc. of a 2 per cent suspension of Flexner's M. V. strain was added an equal amount of diluted antipoliomyelitis horse serum. This was the usual dose, unless otherwise noted. The combination was incubated for one hour at 37.5 C., and 0.1 cc. of the mixture was injected into the first monkey. A second preparation was made in like manner with the serum of horse B and injected into the second monkey. The third monkey was given a mixture of sodium chloride solution and virus in the same proportions as the other 2 animals. These 3 animals constituted a set. In some subsequent experiments, the amount of virus had to be increased because of a decrease in its virulence, the dose injected being from 0.4 to 0.6 cc. of the mixture. All injections were made intracerebrally.

After this, both horses were inoculated with 10 per cent "fortified" virus antigen according to schedule: i. e., March 13, 1937, 50 cc. subcutaneously; March 17, 100 cc. (50 cc. subcutaneously and 50 cc. intramuscularly); March 24, 150 cc. (50 cc. subcutaneously and 100 cc. intramuscularly); March 31 and April 7, 14, 21 and 28, 200 cc. (50 cc. subcutaneously and 150 cc. intramuscularly). The animals became so weak and the clinical response was so severe that after the injections on April 28 immunization was suspended until they had recovered. It was resumed on June 23, when 75 cc. (50 cc. subcutaneously and 25 cc. intramuscularly) of the antigen was given. Subsequent injections were made on June 30, 150 cc. (100 cc. subcutaneously and 50 cc. intramuscularly); on July 7, 200 cc. (100 cc. subcutaneously and 100 cc. intramuscularly), and on July 14, 300 cc. (100 cc. subcutaneously and 200 cc. intramuscularly).

Results: Between June 26, 1937 and Nov. 2, 1938, 27 sets of tests for neutralizing antibodies were made on the serums of horses D and E. The last immunizing dose was given on July 14. The first 9 specimens of serum obtained from horse E, up to Nov. 20, 1937, caused an accelerated production of poliomyelitis in monkeys inoculated intracerebrally with the combination of virus and serum. The animals became ill within a few days and had quadriplegia within three and no later than five days after the injection. Identical results were obtained with the first 3 specimens of blood of horse D. Thus, some product was present in the specimens withdrawn soon after immunization was completed which accelerated the production of the disease when added to virulent virus.

The antibodies were slow in developing and were demonstrable only in the serum of horse D and not until the end of February 1938, approximately a year after the beginning of immunization. At this time it was found that a 1:100 dilution of serum neutralized a 2 per cent suspension of virus. The serum of horse E neutralized the virus only once. A high titer of antibodies of 1:250, in the blood serum of horse D was reached by June 27, 1938. This titer was still found on November 2, while horse E still lacked antibodies even at that late date (table).

In 1 of the 2 horses neutralizing antibodies did not develop. A possible explanation is that this animal had an inherent immunity, which tended to neutralize the specific material when injected and thus prevented the formation of antibodies.

As a matter of collateral interest, it was decided to determine how soon the titer of neutralizing antibodies would drop appreciably in horse D after the first, immunizing, series of injections had been completed. Five sets of neutralizing experiments were made. After a period of about six months, i. e., by May 5, 1939, it was found that the titer had fallen to below 1 : 150.

Experiment 2.—Other collateral experiments were made to determine (1) whether horses which once had been immunized and whose antibody titers had fallen

Results of Neutralization Tests in Experiment 1

Horse Bled	Experiment Date	Amount Injected, Cc.	Horse D * 2% Suspension of Virus Plus Serum 096374	Result	Horse E * 2% Suspension of Virus Plus Serum 096375	Result
6/26/37	7/27/37	0.1	B 1:100	+	B 1:100	+
7/14/37	8/ 6/37	0.1	C 1:50	+	C 1:50	+ (?)
8/19/37	8/21/37	0.1	D 1:50	+	D 1:50	+
8/19/37	9/15/37	0.1	D 1:50	+	D 1:50	+
9/18/37	9/25/37	0.1	E 1:100	—	E 1:100	+
9/18/37	10/ 6/37	0.15	E 1:100	+	E 1:100	+
9/18/37	9/25/37	0.1	E 1:100	—	F 1:100	+
9/18/37	10/ 6/37	0.15	E 1:100	+	F 1:100	+
11/20/37	11/26/37	0.1	G 1:50	+	G 1:50	+
11/20/37	11/26/37	0.1	G 1:50	+ 21 days	G 1:50	+
1/21/38	1/27/38	0.4	H 1:100	+	H 1:100	—
2/23/38	2/28/38	0.4	I 1:100	—	I 1:100	+
3/22/38	3/30/38	0.4	J 1:150	—	J 1:150	+
3/22/38	3/30/38	0.4	J 1:200	—	J 1:200	+
5/27/38	6/ 3/38	0.4	K 1:150	— (?)	K 1:150	+
5/27/38	6/ 3/38	0.4	K 1:200	—	K 1:200	+
6/27/38	6/29/38	0.4	L 1:200	—	L 1:150	+
6/27/38	6/29/38	0.4	L 1:200	—	L 1:200	+
6/27/38	7/16/38	0.5	L 1:200	+ 20 days		
6/27/38	7/16/38	0.5	L 1:250	—		
7/15/38	7/25/38	0.6	M 1:200	+		
7/15/38	7/25/38	0.6	M 1:250	+	N 1:100	+
9/28/38	10/ 1/38	0.45	O 1:250	—	N 1:150	+
9/28/38	10/ 1/38	0.45	O 1:200	—	O 1:100	+
9/28/38	11/ 4/38	0.45	O 1:200	—	O 1:150	± (?)
11/ 2/38	11/ 4/38	0.45	P 1:200	—	O 1:200	+
11/ 2/38	11/ 4/38	0.45	P 1:250	—		

* The capitals indicate the specimens taken in order, A, B, C, etc.

could be reimmunized; (2) whether if once immunized they too had a lag period for the production of antibodies, and (3) whether immunized animals could be kept immunized. Since horse B, previously inoculated with "unfortified" antigen, had not responded with so high a titer of neutralizing antibodies as had A, both horses were reinoculated, this time with the "fortified" antigen.

Each animal was inoculated ten times with virus combined with enteric toxin, according to the following schedule: Dec. 2, 1936, 50 cc. of a 5 per cent suspension; December 9, 100 cc. of a 5 per cent suspension; December 16, 150 cc. of a 5 per cent suspension; December 23, 200 cc. of an 8 per cent suspension; December 30, January 6, 13, 20 and 27 and February 3, 200 cc. of a 10 per cent suspension. In each instance half of the total dose was given intramuscularly and half subcutaneously.

The animals were bled on February 21, March 17 and April 18.

Six sets of neutralization tests were done. The neutralizing antibody titer of horse A's blood serum returned to the same level as previously recorded (1935-1936); it was significant that although no neutralizing antibodies were found in the first specimen of serum of horse B, taken on Feb. 21, 1937, or eighteen days after the last immunizing injection, no accelerating

factor was present. The second and third specimens from both animals, taken on the forty-second and the seventy-fourth day after immunization had been completed, contained neutralizing antibodies with a titer of at least 1 : 350.

Thus, these 2 horses which had been immunized previously could be reimmunized to a point where potent neutralizing antibodies could again be found in their blood serums. There was no marked lag in production of antibodies and no factor in the blood serum that accelerated the production of experimental poliomyelitis in monkeys.

Experiment 3.—Since the horses were available, it was decided to do a collateral experiment not entirely pertinent to the original objective and to determine whether horses A and B could be kept immunized to the point where their blood serums would continually show the same high titer of neutralizing antibodies. After a full bleeding, both animals were reinoculated on April 28 and May 5, 12 and 19, 1937. The inoculum in each instance was 200 cc. of 10 per cent "fortified" virus—one half given subcutaneously and the other intramuscularly. The horses were bled on June 26, Aug. 18 and Nov. 13, 1937 and on Feb. 7, March 4, April 6 and Sept. 28, 1938.

Twelve sets of neutralizing tests were made between June 26, 1937 and Sept. 28, 1938. Potent neutralizing antibodies, with a titer of at least 1 : 250, were found each time the blood serums were tested—and this despite the fact that the total amount of virus used in the neutralizing tests of 1938 had to be increased to 0.4 cc. for each injection because of a decrease in the virulence of the strain.

Thus, these 2 animals (A and B) could be immunized to a point where neutralizing antibodies in high titer were found in their blood serums, and they could be kept in that immunized state for at least two years by repeated injections of "fortified" virus.

COMMENT

Diphtheria and other antitoxins are usually present in the blood of horses approximately two to three weeks after the last injection of the immunizing antigen. In contrast, there is a lag in the production of neutralizing antibodies against poliomyelitis after injections of "fortified" virus. This is evidenced by the fact that it took a longer time for these antibodies to develop in the experimental animals—almost ten months in the first experiments of 1935 and nearly twelve months in the experiments reported in this paper. This is not the usual experience in the production of antitoxins. It may explain why some monkeys and some human beings lack neutralizing antibodies immediately after recovery from poliomyelitis. It may well be that the bleedings were made at the wrong time during convalescence.

It has also been demonstrated again that the first specimens of blood, taken a short time after immunization had been completed, contained an accelerating factor. Antibodies tend to disappear quickly; however, if an animal has once developed antibodies and after a rest is reinoculated, the titer goes back up quickly and no accelerating factor is found in the blood serum. Such a response is comparable to that seen when tetanus toxoid is injected into a human being previously immunized with tetanus toxoid.

This poliomyelitis antiserum, although virucidal and tested clinically, cannot be recommended for therapeutic purposes, since there is no evidence that it has any value after the virus has become fixed in monkeys.

SUMMARY

Neutralizing antibodies against poliomyelitis virus were produced in the blood serum of 1 of 2 horses immunized with a "fortified" antigen (poliomyelitis virus and a paratyphoid-colon bacillus filtrate [enteric toxin]).

The production of neutralizing antibodies in this animal was not immediate. The first horse blood serums obtained acted as accelerators rather than as neutralizers of poliomyelitis virus, since the infection was produced more quickly in Macaca mulatta monkeys inoculated with serum and virus than in control animals given injections of solution of sodium chloride and virus.

After a horse once began to show neutralizing antibodies, its blood serum could be kept in a state of high titer by frequent injections of "fortified" poliomyelitis virus, and there were no accelerating factors.

When the horses that previously (1935-1936) had developed antibodies after a series of immunizing injections were allowed to rest, their titers of neutralizing antibodies fell. When they were reinoculated, no accelerating factor was found in the early specimens of blood serum, and antibodies developed more quickly than when the antigen was originally injected.

THE "VISIBLE TUBERCULIN PATCH TEST"

A NEW IMPROVEMENT

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The advantages of the tuberculin patch test are obvious: It is absolutely painless and hence eliminates the elements of fear, wherefore it is especially adapted for testing children; it requires no lancets or borers (as in the Pirquet[1] test), no syringes and needles (as in the Mantoux[2] test) and no rubbing of tuberculin ointment into the skin (as in the Moro[3] test).

The long-felt need of a simple and painless method of testing for tuberculosis evidenced itself by the numerous publications dealing with the tuberculin patch test and by its wide acceptance.

The patch test, however, has one disadvantage when compared with the Pirquet, Mantoux and Moro tests: The area of reaction remains concealed while the patch is in place, so that it cannot be followed during the phases of its development. In other words, the test is a "blind test."

DISADVANTAGES OF A "BLIND TEST"

With the Pirquet, Mantoux and Moro methods of testing a positive reaction can be observed as soon as it is formed, whereas with the ordinary tuberculin patch test there is no way of judging when the strip of adhesive tape should be removed to determine the results, since the time required for the tuberculin to act varies in different subjects and under diverse conditions.

If the strip is removed too early, a positive reaction may be missed. On the other hand, if the tuberculin-treated adhesive plaster remains in intimate contact with the skin long after the reaction has developed, it may produce undesirable inflammatory reactions.

Most observers believe that the strip of adhesive plaster should be removed after forty-eight hours and the results interpreted forty-eight hours later. Others are of the opinion that a longer time is required. Taylor[4] maintained that the patch should remain in contact with the skin for seventy-two hours. Savage[5] found some positive reactions were not revealed until ninety-six hours had passed. Similarly Neiman, Rosenthal and Motel[6] stated that accurate reading may be obtained best at ninety-six hours. Palin[7] called attention to the fact that in some cases the reaction may not become readable until five to seven days after the application of the patch.

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1. von Pirquet, C.: Tuberculindiagnose durch kutane Impfung, Berl. klin. Wchnschr. **20**:22, 1907.
2. Mantoux, C.: Intra-dermo-réaction de la tuberculine, Compt. rend. Acad. d. sc. **147**: 355, 1908.
3. Moro, E.: Ueber eine diagnostische verwertbare Reaktion der Haut auf Einreibung mit Tuberkulinsalbe, München. med. Wchnschr. **55**:216, 1908.
4. Taylor, G.: Tuberculin Patch Test: A Comparison with the Mantoux Intracutaneous Test, Am. Rev. Tuberc. **40**:236 (Aug.) 1939.
5. Savage, C. L.: Comparison of Reactions to Different Tuberculins in the Same Individuals, Am. Rev. Tuberc. **43**:527 (April) 1941.
6. Neiman, I. S.; Rosenthal, S. R., and Motel, W. G.: Tuberculin Patch Test on BCG vaccinated and Control Children, J. Pediat. **19**:540 (Oct.) 1941.
7. Palin, A.: Tuberculin Patch Test, Brit. M. J. **1**:1006 (May 13) 1939.

On the other hand, if the tuberculin-treated adhesive plaster is not removed in time, there may arise unpleasant results. Thus, in Palin's [7] series there were noted some severe local cutaneous reactions with extreme pruritus. Court [8] called attention to painful vesiculation occurring in some cases. Similar observations were made by Hart.[9]

The "blind" test is especially disadvantageous when used on persons with active tuberculosis. It was therefore suggested that tuberculin patches be applied at fractional periods; that is, that patches be removed at six, twelve or twenty-four hours and if there were no reactions, other patches be applied. But this would entail additional expense if commercial patch tests were used. It would mean more visits to the clinic or office, more work and considerable loss of time.

Then, too, it cannot be said that repeated patch tests with concentrated tuberculin are entirely harmless to persons with tuberculosis. Schwartzman, Dragutsky and Rook [10] noted systemic reactions, such as elevation of temperature, in tuberculous patients as a result of repeated tuberculin patch tests.

Because of the disadvantages of a "blind patch test" and the desirability of one in which the progress of the reaction can be observed at any time while the patch is still *in situ* without disturbing its effectiveness, the following method has been devised. It will be referred to as the "visible tuberculin patch" test.

METHOD

1. A strip of adhesive plaster 1¼ inches (3 cm.) wide and 3½ inches (9 cm.) long is placed on a smooth surface, adhesive side down.

2. In the center of each third of the strip, incomplete circles are cut (fig. 1) so that a hinged flap to serve as a lid is obtained, with the uncut lower chord operating as a hinge.

3. The nonadhesive surface of a second strip of adhesive plaster is moistened with tuberculin (with the aid of a medicine dropper or a tiny brush) and allowed to dry. It is then cut into ¼ inch (0.6 cm.) squares (by means of a razor blade or sharp knife).

4. One of these ¼ inch squares is picked up with a forceps and placed in the center of the adhesive surface of each of the outer lids so that the nonadhesive surface, previously treated with tuberculin, is in contact with the skin when the patch is applied.

5. Another ¼ inch square of adhesive plaster which has not been treated with tuberculin is applied to the middle lid as a control (fig. 2).

6. Instead of adhesive plaster a piece of gauze may be moistened with tuberculin, allowed to dry and then cut into ¼ inch squares and similarly applied to the outer lids. As a control a ¼ inch square of gauze not treated with tuberculin may be applied to the central lid.

7. The adhesive surface of the entire strip may be covered with crinoline and kept for future use.

8. The skin of the forearm, chest or back is cleaned with ether or acetone and the patch applied.

9. At various intervals, the lids may be opened for inspection and then closed. As an extra precaution it may be advisable to press on the upper and lower

8. Court, S. D. M.: A Comparative Study of the Tuberculin "Patch Test" and the Intracutaneous Mantoux Test in Childhood, Brit. M. J. **1**:824 (April 22) 1939.

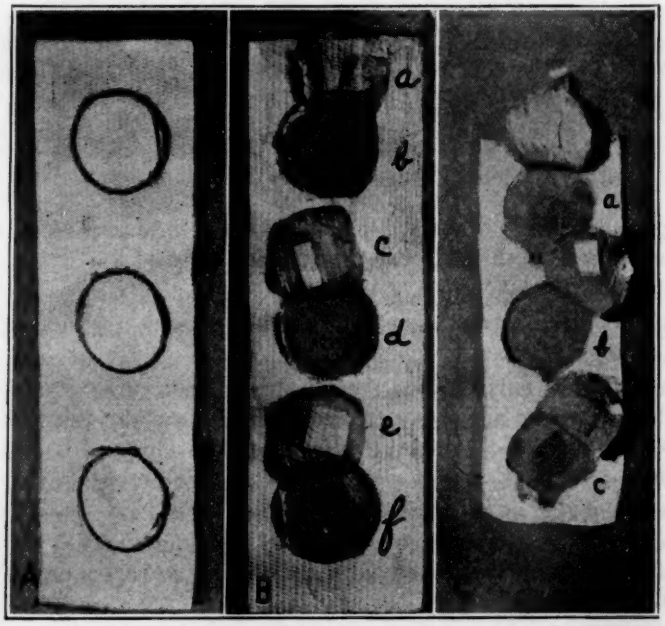
9. Hart, F.: Tuberculin Patch Tests in Children, Lancet **2**:609 (Sept. 10) 1938.

10. Schwartzman, J.; Dragutsky, D., and Rook, G.: Tuberculin Patch Test, J. Pediat. **20**:50 (Jan.) 1942.

ends of the adhesive strip with the left index finger and thumb while opening or closing the lids with the right hand. Also, in closing the lid it is important to press it down so that it is in close contact with the skin.

MODIFICATIONS

Because of the simplicity of construction, this test naturally lends itself to numerous modifications: The lid may be of any shape, triangular instead of circular so that the base of the triangle may act as the hinge, while the narrow top can serve as the tab by which the lid may be opened. Or the lid may be in the shape of a square. Furthermore, the lid may be located to open in any direction, e. g., toward the side of the main strip. Also, each lid can be cut with a tab (fig. 3) at the forward edge, which can be folded to form a small welt which will provide a grip facilitating the opening of the lid.



Visible tuberculin patch test. *A*, flaps cut but not everted. *B*, test strip in use: (*a*) everted lid which was previously treated with tuberculin; (*b*) positive cutaneous reaction; (*c*) everted lid not treated with tuberculin (used as a control); (*d*) no reaction; (*e*) everted lid previously treated with tuberculin; (*f*) positive reaction. *C*, positive reaction after twenty hours (lids everted by means of rolled-up flaps): (*a*) positive cutaneous reaction; (*b*) control; (*c*) positive reaction.

The number of lids may be increased, and if necessary to accommodate them a larger strip of adhesive plaster may be used. This would be especially applicable for research purposes, e. g., to study effects of different dilutions of tuberculin.

Furthermore, a strip of the adhesive plaster could be perforated in several places and applied to the skin and the openings covered by flaps containing the testing material and the controls; or the main perforated strip could be covered with such flaps before being applied to the skin and the flaps could be lifted in order to inspect the reacting area and then put back in place.

It will be noted that the nonadhesive surface of the plaster was used as the medium for absorbing tuberculin, partly because the tuberculin-treated square

can be made to stick on any surface. Advantage can be taken of this fact in case it is wished to use some nonadhesive material, such as cellophane, silk, gauze or surgeon's lint, in order to avoid irritation of the skin of a person who is sensitive to the adhesive substance. Under such conditions the tuberculinized adhesive plaster can be placed on some nonirritating material and this applied to the strip.

The various mediums which can be used for absorbing tuberculin are legion and are of secondary importance, since they do not alter the fundamental principle of the tuberculin patch test. These mediums include cotton, gauze, blotting paper, plain paper, filter [11] paper, cloth, wool, surgeon's lint and ointment.[12] The use of various mediums for absorbing testing material are described in old [11a] as well as in more recent [13] textbooks on allergy. For many years I have been experimenting with various mediums for absorbing tuberculin, and I have found no superiority of one over the other. They can be used interchangeably without altering the efficiency of the test. In fact, thousands of tests were performed without the aid of a medium, by simply moistening the intact skin with tuberculin and covering the area with a strip of adhesive plaster or by first moistening the strip with the tuberculin and then applying it to the skin, as described in a previous communication.[14] (The tuberculin-treated adhesive plaster may be used wet or dry.)

As a control the middle lid can be used plain or treated with glycerin broth or bouillon (without tuberculin).

Although Koch's old tuberculin was used as the testing agent, the pure protein derivative can also be employed for this purpose.[15] It was not within the province of the work reported in this paper to make a comparative study of the various makes of tuberculin. Since 1931 I have been using Koch's old tuberculin, supplied by the Bureau of Laboratories of the New York Department of Health, in patch tests and have found it quite satisfactory, the results comparing favorably with those obtained with a 1 : 1,000 dilution (0.1 mg.) in a Mantoux test. Recent studies by Reisman and Grozin [16] have shown that paper toweling treated with Koch's old tuberculin gave reliable results in patch tests. It is hoped that by the use of the "visible tuberculin patch test" it will be possible to evaluate the various kinds of tuberculin, since one can use a strip of adhesive plaster with multiple lids, each of them treated with a different make of tuberculin, and compare the results. It is evident that the ideal tuberculin patch test is one which, although reliable, requires the smallest quantity of the least concentrated tuberculin, as well as the shortest period of contact with the subject tested.

ADVANTAGES OF THE "VISIBLE TUBERCULIN PATCH TEST"

Regardless of the large number of modifications which may be used in its construction, the advantages of a "visible tuberculin patch test" are obvious:

1. This test makes it possible to observe the reaction to tuberculin at any time the patch is still in place without in any way reducing its efficiency. Further-

11. (*a*) Bray, G. W.: Recent Advances in Allergy, ed. 2, Philadelphia, P. Blakiston's Son & Co., 1934. (*b*) Vollmer, H., and Goldberger, E. W.: A New Tuberculin Patch Test, Am. J. Dis. Child. **54**:1019 (Nov.) 1937.

12. Habetin, P.: Die Tuberkulinsalbenpflasterprobe, Wien. klin. Wchnschr. **41**:703 (May 17) 1928. Wolf, E.: Tuberculin Ointment Patch Test, Am. J. Dis. Child. **47**:764 (April) 1934.

13. Tuft, L.: Clinical Allergy, Philadelphia, W. B. Saunders Company, 1937, p. 461.

14. Grozin, M.: The Tuberculin Patch Test: A Diagnostic Aid in Tuberculosis, Am. J. Dis. Child. **46**:17 (July) 1933.

15. Furcolow, M.: Efficiency of the Patch Test, Pub. Health Rep. **56**:51 (Dec. 19) 1941.

16. Reisman, H. A., and Grozin, M.: The Tuberculin Test, Am. J. Dis. Child. **62**:1197 (Dec.) 1941.

more, regardless of the number of times the lids are opened and closed, the same tuberculin returns into contact with the skin in the same area.

2. Instead of waiting two or three days before taking off the strip and then another two days for the nonspecific reaction from the adhesive to clear up, as one does now (regardless of whether the subject is an early or late reactor to tuberculin), it will be possible by simply opening the lids to view a positive reaction as soon as it is formed (fig. 3). The test will save considerable time, which may be of value when tuberculosis has to be ruled out quickly, for purpose of diagnosis and treatment.

3. It will be unnecessary to repeat the entire test in case of doubt or when it is felt that more time should be allowed for the tuberculin to act. In such cases the patch can be left in place for a longer period. Any intelligent layman or nurse will be able to recognize a positive reaction. It will obviate extra visits to the office or clinic and unnecessary expense. It will also in some cases shorten the period during which the arm, chest or back cannot be bathed.

4. It will be easier to determine whether the reaction is positive or negative, because the reacting area is surrounded by the strip of adhesive plaster, with which it is in sharp contrast, instead of by skin, which may have blotches, hair follicles, pimples, discolorations or blemishes that interfere with the reading of the results.

5. For persons who are strongly allergic to tuberculin or sensitive to adhesive plaster, it will obviate some unpleasant reactions, such as itching and vesiculation, which result from keeping the strip on the skin longer than is actually required for obtaining a positive reaction. The entire strip can be taken off as soon as opening of the lids reveals a positive reaction.

6. In some cases of active tuberculosis it will eliminate the danger of systemic reaction caused by the use of a too highly concentrated tuberculin, because contact of the tuberculin with the human body will be reduced to a minimum.

7. It will be possible to add tuberculin to the lids without disturbing the entire strip when it is felt that more is required for further testing.

8. Since some persons are known to react to tuberculin earlier than others, the test will enable investigators to study the period of latent reaction in different subjects under various conditions, and to determine possible significance.

9. It will aid in producing a quantitative patch test by showing the amount and the concentration of tuberculin as well as the time required to obtain a positive reaction. Such quantitative studies can be made by means of a longer strip with many lids. Different concentrations of tuberculin can be used and the results compared.

10. Since tuberculin cannot be identified chemically, but only by its biologic reaction, it will by this method be possible to determine the efficiency and concentration of tuberculin. This can be done by using tuberculin of different strengths on multiple lids and observing the effects.

11. Similarly, it will enable physicians to determine the relative merits of the various makes of tuberculin for patch tests.

12. It will facilitate the study of how the evolution of the reaction to the tuberculin patch test is influenced by various diseases, such as influenza,[17] measles, pleurisy,[18] syphilis [19] and cancer.

17. Bloomenfield, A., and Matier, J. G.: Changes in Skin Sensitivity to Tuberculin During Epidemic Influenza, Am. Rev. Tuberc. **3**:166 (March) 1919.

(Footnotes continued on next page)

13. It will aid in the study of the influence on the tuberculin reactions of various factors, such as drugs (e. g., epinephrine [20] and thyroxin [21]) and ultraviolet rays.

14. These various advantages will permit this test to be modified according to individual needs. It will therefore lend itself to use in research.

15. The same strip can be used for testing with allergens, chemical and other substances.

SUMMARY AND CONCLUSION

To overcome the disadvantages of the tuberculin patch test of today, which conceals the area of reaction while the patch is in situ, the following improvement has been devised: Three incomplete circles are cut on a strip of adhesive plaster, forming flaps or lids, with the lower poles acting as hinges. The outer lids are treated with tuberculin. The middle lid, without tuberculin, acts as a control. The entire strip is applied to the skin. The areas of reaction are observed by lifting the lids.

Advantages of the visible tuberculin patch test are: It makes it possible to view the results at any time without removing the strip. This may shorten the period required for reading the reaction as well as prevent some untoward local and systemic effects resulting from prolonged contact of tuberculin and adhesive plaster with the skin. On the other hand, if the results are doubtful, the strip can be kept on the skin for a longer time, and repetition of the entire test will not be necessary. This method will facilitate study of the evolution and the latent period of reactions to tuberculin and of how they are influenced by drugs, chemicals, disease, temperature and other factors. It may also help make it an individualized and quantitative test, as well as enable investigators to determine the concentration and efficiency of various makes of tuberculin. The reaction will be easier to interpret than that in an ordinary patch test, since the test site will be in sharp contrast with the uniform color of the adhesive plaster instead of the surrounding skin, with possible discolorations and blemishes.

3619 Bowne Street.

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RESPONSE TO A STIMULATING INJECTION OF TETANUS TOXOID

REPORT OF A STUDY ON CHILDREN PREVIOUSLY IMMUNIZED WITH COMBINED DIPHTHERIA AND TETANUS TOXOID

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The purpose of this article is to report the response to a stimulating dose of tetanus toxoid in children previously (one and one-half to two and one-half years) immunized with combined diphtheria and tetanus toxoid, alum precipitated. The report of the initial antitoxin response in the same group of children has already been published.[1] The value of active immunization against tetanus is being rapidly recognized by members of the medical profession, and even among the nonmedical population there are many requests for protection against lockjaw.

In evaluating the results of a study of this sort, one is handicapped by not knowing the exact relationship between circulating antitoxin and the total immunologic status of a person in any one instance. Such factors as the size of the infecting dose of tetanus spores, the total quantity of blood serum present and the antigenic effect of liberated toxin are unknown quantities when one is speaking of a subject's immunity. When one studies the antitoxin level of the serum, then one admittedly is dealing with but one phase of the total immunity picture. While no attempt will be made here to set a "protective level" of antitoxin, for purposes of better evaluation of reports such as this we can say that it has been variously assumed that 0.01 or 0.1 U.S.P. unit of antitoxin per cubic centimeter of serum is associated with probable protection against clinical tetanus.[2] A practical test of active immunity is occurring in the present war, in which it has been used in a massive number of instances. The results of this test are by no means complete, but such as are available are very encouraging (reports from Dunkirk, from France and from Pearl Harbor).[3] Statistics from the millions in the armed forces will mean more in a practical way than those from the smaller number of subjects in clinic groups, however carefully the latter may be studied.

So far as we are aware there have been reports of tetanus in 6 persons who have received active immunization, two of which are somewhat questionable. Simon and Patey [3c] reported the case of a French soldier who had received fluid toxoid and later had mild tetanus, from which he recovered. Boyd and Maclennan [3e] reported 5 cases of tetanus (3 of them fatal) in immunized persons, but of the 5

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cases 1 is based on hearsay and another is not conclusive. We can add another case from the United States Navy. A sailor received the routine immunization of the Navy, consisting of two injections of alum-precipitated tetanus toxoid, which in this instance were given six weeks apart. Sixteen weeks after the second injection he sustained a crushing injury to both feet while aboard ship. He was admitted to a local naval hospital twenty-two days later with the typical findings of a low grade tetanus. He was given repeated doses of antitoxin, with disappearance of all symptoms two weeks later. Contrast this incidence of 7 cases plus possibly even a few more unreported ones, with statistics from the last war, without active immunization, as reported by Hall [4]:

Military Force	Incidence of Tetanus per 1,000 Wounded	Mortality Per Cent
British Expeditionary Force, 1915-1919	1.5	50.0
German, all fronts, 1914	3.8	75.0
United States, 1917-1918	0.2	11.1

Marvel and Parish [5] reported 2,500 cases of tetanus in the British Army between 1914 and 1918, with a mortality of 43.2 per cent.

In spite of this, the current civilian practice still remains the administration of tetanus antitoxin with each injury, since no attempt has been made to offer active immunization except in pediatric groups and the armed forces.

METHOD OF STUDY

Children who had been infants in the well baby clinic when receiving basic immunity and a few young children from the general clinic form the basis for this study. The majority were just under 1 year of age at the time of primary immunization; hence when the recall study was done, one and one-half to three and one-half years later, the age range of this group was from 2 to 4½ years. A few children between 5 and 10 years are also included, as they had received basic immunity either at the same time as younger siblings or in the allergy clinic. The basic immunization consisted of two or three injections of 1 cc. of combined diphtheria and tetanus toxoid, alum precipitated.[6] At the time of recall a sample of blood was taken and a stimulating dose of 0.5 cc. of tetanus toxoid, alum precipitated, was given intramuscularly.[6] One week later a second sample of blood was obtained for estimation of antitoxin. All determinations of antitoxin were made by mixing varying amounts of the patient's plasma with a fixed amount of tetanus toxin from the National Institute of Health and injecting this mixture into guinea pigs.[7] The survival of the animal indicates an excess of antitoxin for the level tested. Death before one hundred and twenty hours indicates less than that level of antitoxin, and survival for one hundred and forty-four hours with symptoms of tetanus indicates a close approximation of the level tested.

Antitoxin titers are reported in U. S. P. units per cubic centimeter of plasma. Tests were made at the following levels: 0.001, 0.003, 0.01, 0.03, 0.1, 0.3, 1.0, 3.0, 10.0, 30.0 and 60.0 units per cubic centimeter. When the titer did not exactly coincide with one of these levels, it was reported as lying between two adjacent levels.

The seven day interval was chosen because it is the lower limit of the average incubation period of tetanus. In other words, we wanted to know what antitoxin level would be present at a time when tetanus might develop provided the hypothetic injury occurred just prior to administration of the stimulating dose of toxoid.

RESULTS OF RECALL INJECTION OF ALUM-PRECIPITATED TETANUS TOXOID

In table 1 are presented the results for those children who had had titers taken shortly after completion of basic immunization as well as just before and seven days after they received the stimulating dose of toxoid. In table 2 results are given for

4. Hall, W. W.: Ann. Int. Med. **14**:565, 1940.
5. Marvel, D. M., and Parish, H. J.: Brit. M. J. **2**:891, 1940.
6. Material used in this study was the combined diphtheria and tetanus toxoid, alum precipitated, and the tetanus toxoid, alum precipitated, of Eli Lilly & Co.
7. Titrations on guinea pigs were done by us at the Cutter Laboratories, Berkeley, Calif.

TABLE 1.—*Recall Data (with Previous Titers)*

Three Injections of 1 Cc. of Diphtheria and Tetanus Toxoid, Alum Precipitated, for Basic Immunity							
Subject No.	Weeks Between 1st and 3d Injection	Months After Last Injection	Antitoxin Titer, Units per Cc. of Plasma	Months After Last Injection	Antitoxin Titer, Units per Cc. of Plasma	Days After Recall Injection of 0.5 Cc. of Alum-Precipitated Tetanus Toxoid	Antitoxin Titer, Units per Cc. of Plasma
4	9	3	>0.01 <0.03	42	0.001	7	>0.01 <0.03
	..	9	>0.03 <0.1				
345	14	2 after 2d injection	<0.01	23	0.001	7	>0.03 <0.1
198	8	2½	0.1	22	0.03	7	>0.3 <1.0
288	11	4	>0.3 <1.0	21	0.1	5	>0.3 <1.0
10	10	3	>0.1 <0.3	26	>0.01 <0.03	7	>1.0 <3.0
116	8	1½	0.1	24	0.01	7	>1.0 <3.0
474	6	3	0.03	17	>0.03 <0.1	7	>1.0 <3.0
97	8	2	>1.0 <3.0	35	0.1	21	>1.0 <3.0
549	8	3½	0.01	17	0.003	7	>1.0 <3.0
121	9	2	>0.1 <0.3	34	0.03	7	>1.0 <3.0
329	10	2	<1.0 >3.0	24	>0.3 <1.0	7	>1.0 <3.0
357	12	2	>0.3 <1.0	22	0.03	7	>1.0 <3.0
508	10	3	>0.03 <0.1	20	>0.003 <0.01	6	>1.0 <3.0
509	10	3	0.03	20	0.01	6	>1.0 <3.0
340	8	2	>0.03 <0.1	24	0.03	7	>1.0 <3.0
519	8	2	0.03	21	>0.003 <0.01	7	>1.0 <3.0
408	10	3	0.03	21	>0.003 <0.01	7	>1.0 <3.0
369	9	4	>0.3 <1.0	22	0.1	7	3.0
8	9	3	>0.1 <0.3	25	0.03	7	3.0
24	8	6	0.03				
		15	>0.03 <0.1	29	0.01	7	3.0
360	9	2	>0.1 <0.3	22	0.01	7	3.0
2	9	6	>0.1 <0.3	25	>0.01 <0.03	7	>3.0 <10.0
51	8	4	>0.3 <1.0	24	>0.03 <0.1	7	>3.0 <10.0
56	9	2	>1.0 <3.0	23	0.1	7	>3.0 <10.0
178	9	6	>1.0 <3.0	21	>0.3 <1.0	7	>3.0 <10.0
158	8	2	>1.0 <3.0	22	>0.1 <0.3	7	>3.0 <10.0
161	9	3½	0.1	21	0.1	7	>3.0 <10.00
170	8	3	>1.0 <3.0	21	0.1	7	>3.0 <10.00
182	8	3	>0.1 <0.3	23	>0.1 <0.3	7	>3.0 <10.00
163	8	2	>0.1 <0.3	22	>0.1 <0.3	7	>3.0 <10.00
191	13	3	>0.3 <1.0	20	>0.03 <0.1	7	>3.0 <10.00
188	9	2	>1.0 <3.0	21	>0.1 <0.3	7	>3.0 <10.00
363	11	4	>1.0 <3.0	12	>0.3 <1.0	7	>3.0 <10.00
248	8	2	>0.3 <1.0	22	0.03	9	>3.0 <10.00
232	9	4	>0.3 <1.0	23	0.01	7	>3.0 <10.00
201	8	2	>0.1 <0.3	27	0.01	7	>3.0 <10.00
216	9	2	0.3	26	>0.1 <0.3	7	>3.0 <10.00
303	8	2	>0.3 <1.0	22	>0.03 <0.1	7	>3.0 <10.00
283	9	5	>0.3 <1.0	24	<0.3	7	>3.0 <10.00
309	8	2	>0.3 <1.0	23	>0.03 <0.1	11	>3.0 <10.00
144	23 (4-19)	2½	>10.0 <30.0	28	>0.3 <1.0	9	>3.0 <10.00
145	8	2	>1.0 <3.0	32	>0.1 <0.3	7	>3.0 <10.00
151	8	2	>1.0 <3.0	32	>0.1 <0.3	7	>3.0 <10.00
140	11	2½	>1.0 <3.0	31	0.03	7	>3.0 <10.00 *
308	8	2	>0.3 <1.0	22	>0.001 <0.003	7	>3.0 <10.00
138	10	3	>1.0 <3.0	31	0.3	7	>3.0 <10.00
139	8	1	>1.0 <3.0	32	0.03	7	>3.0 <10.00
115	8	2	>0.3 <1.0				
		12	>0.1 <0.3	33	0.1	7	>3.0 <10.00
118	9	2	>1.0 <3.0	33	>0.1 <0.3	7	>3.0 <10.00
89	8	2	3.0	35	>0.1 <0.3	7	>3.0 <10.00
102	8	2	>1.0 <3.0	34	>0.1 <0.3	7	>3.0 <10.00
500	9	3	0.03	16	>0.03 <0.1	7	>3.0 <10.00
76	7	2	>1.0 <3.0	36	>0.03 <0.1	7	>3.0 <10.00
322	9	2	>0.3 <1.0	23	0.03	7	>3.0 <10.00
327	8	2	0.1	24	0.1	7	>3.0 <10.00
341	9	2	0.1	23	0.01	7	>3.0 <10.00
352	7	2	>0.3 <1.0	23	>0.1 <0.3	7	>3.0 <10.00
346	10	4	>0.3 <1.0	23	>0.1 <0.3	7	>3.0 <10.00
353	14	2	>1.0 <3.0	25	>0.1 <0.3	7	10.0
555	14	2	>3.0 <10.0	22	>0.1 <0.3	7	10.0
9	36 (31-5)	3	>1.0 <3.0	19	1.0	7	10.0
25	8	3	1.0	24	>0.1 <0.3	7	10.0
26	10	1½	>1.0 <3.0	24	>0.1 <0.3	7	10.0
46	9	1½	>1.0 <3.0	24	>0.1 <0.3	7	10.0
254	8	2	>3.0 <10.0	23	0.03	7	10.0
277	8	3	>0.3 <1.0	23	0.1	7	10.0
299	8	2	>0.3 <1.0	22	0.1	7	10.0
152	8	3½	>1.0 <3.0	32	>0.1 <0.3	7	10.0
		9	>0.1 <0.3				
310	8	2	>0.1 <0.3	23	0.03	11	>10.0 <30.0
133	7	2	>1.0 <3.0	32	>0.003 <0.01	7	>10.0 <30.0
141	8	2	>1.0 <3.0	19	>0.1 <0.3	7	>10.0 <30.0
266	11	2	>1.0 <3.0	23	>0.3 <1.0	7	>10.0 <30.0
244	10	2	>0.1 <0.3	24	0.03	9	>10.0 <30.0
290	10	2	>1.0 <3.0	22	>0.03 <0.1	11	>10.0 <30.0
48	8	1½	>0.3 <1.0	24	0.03	7	>10.0 <30.0

> indicates "more than"; < indicates "less than"; where no such symbol preceded the antitoxin titer it was found to be exactly at that level.

* Titer the same at seven days and seven weeks.

TABLE 2.—*Recall Data (No Previous Titer)*

Three Injections of 1 Cc. of Diphtheria and Tetanus Toxoid, Alum Precipitated, for Basic Immunity

Subject No.	Weeks Between 1st and 3d Injection	Months After Last Injection	Antitoxin Titer, Units per Cc. of Plasma	Days After Recall Injection of 0.5 Cc. of Alum-Precipitated Tetanus Toxoid	Antitoxin Titer, Units per Cc. of Plasma
63	8	36	>0.1 <0.3	7	>0.3 < 1.0
230	8	24	>0.1 <0.3	4	0.3
50	25 (6-19)	20	>0.1 <0.3	7	> 1.0 < 3.0
169	9	21	>0.1 <0.3	7	> 1.0 < 3.0
184	8	22	0.003	7	> 1.0 < 3.0
274	8	23	>0.06 <0.1	7	> 1.0 < 3.0
316	19	20	>0.03 <0.1	7	> 1.0 < 3.0
361	8	23	0.03	7	> 1.0 < 3.0
362	8	23	>0.06 <0.1	7	3.0
7	9	25	>0.01 <0.03	7	> 3.0 <10.0
52	8	23	>0.1 <0.3	7	> 3.0 <10.0
179	8	20	0.03	7	> 3.0 <10.0
168	9	21	>0.1 <0.3	7	> 3.0 <10.0
190	16	20	>0.1 <0.3	7	> 3.0 <10.0
225	8	24	0.03	7	> 3.0 <10.0
280	8	23	0.01	7	> 3.0 <10.0
298	8	22	>0.03 <0.1	7	> 3.0 <10.0
155	8	30	>0.1 <0.3	7	> 3.0 <10.0
315	19	20	0.1	7	> 3.0 <10.0
68	8	36	0.3	7	> 3.0 <10.0
287	16	23	>0.1 <0.3	7	> 3.0 <10.0
334	8	23	0.1	7	> 3.0 <10.0
347	8	23	0.03	7	> 3.0 <10.0
57	11	23	>0.03 <0.1	7	>10.0 <30.0
189	16	20	>0.03 <0.1	7	>10.0 <30.0
202	8	21	>0.3 <1.0	7	>10.0 <30.0
306	13	20	0.1	7	>10.0 <30.0
226	11	24	>0.06 <0.1	7	>10.0 <30.0
58	11	23	>0.1 <0.3	7	>30.0 <60.0

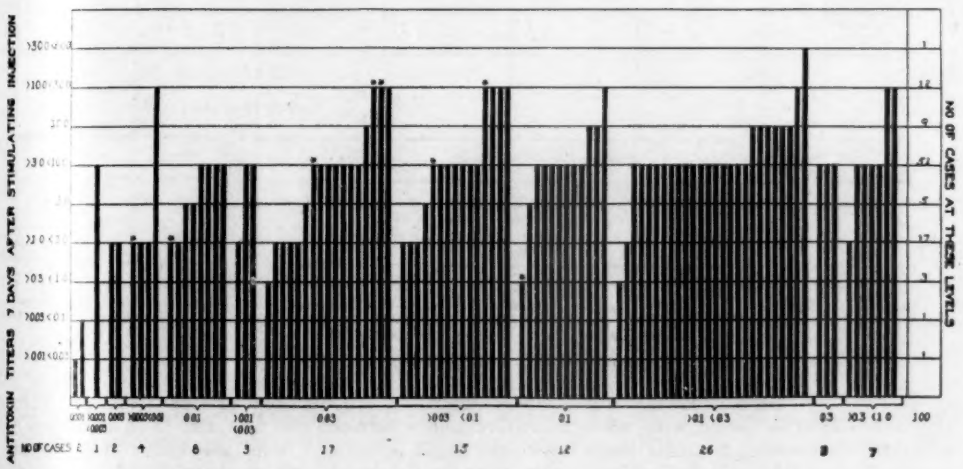
ANTITOXIN TITERS 7 DAYS AFTER STIMULATING INJECTION
NO OF CASES AT THESE LEVELS
TETANUS ANTITOXIN TITERS BEFORE STIMULATING INJECTION

Chart 1.—Recall data. Tetanus antitoxin titers in 100 cases, showing the level seventeen to thirty-six months (except for 1 each at twelve, sixteen and forty-two months) after completion of the basic immunization with three injections of combined diphtheria and tetanus toxoid, alum precipitated (seven to twenty-three weeks between the first and the third injection) and the height of the rise in tetanus antitoxin titers seven days after a stimulating dose of 0.5 cc. of tetanus toxoid, alum precipitated. The following irregularities, indicated by *, are to be noted: Blood was withdrawn five days after stimulation from 1 child in the 0.1 unit group; blood was withdrawn six days after stimulation from 1 child in the 0.003 to 0.01 unit group and from 1 in the 0.01 unit group; blood was withdrawn nine days after stimulation from 2 children in the 0.03 unit group; blood was withdrawn eleven days after stimulation from 1 child in the 0.03 unit group and from 2 in the 0.03 to 0.1 unit group.

those for whom titers were obtained only just before and seven days after the recall injection. There were 75 in the former group and 29 in the latter, making 104 in all. Chart 1 is a recapitulation of tables 1 and 2, with the recall data presented in

a different manner. Data for patients 97, 9, 230 and 50 were omitted from chart 1 because of irregular time elements, variations in intervals either between injections of basic immunization or between recall injection and subsequent titer. The periods between the completion of basic immunity with combined toxoid and the recall, or stimulating, injection of tetanus toxoid ranged between seventeen and thirty-six months, with the exception of 1 interval of twelve, 1 of sixteen and 1 of forty-two months. The majority were between twenty and thirty-six months.

Chart 2 presents data on antitoxin levels following basic immunization only and does not include any recall data.

In table 1 it will be seen that the lowest poststimulation titer was between 0.01 and 0.03 unit (case 4). This was that of a child who also had one of the lowest titers before stimulation (0.001 unit) and, in addition, the longest interval between basic immunity and recall injection (forty-two months). For this same patient titers taken three and nine months after completion of basic injections had been found to

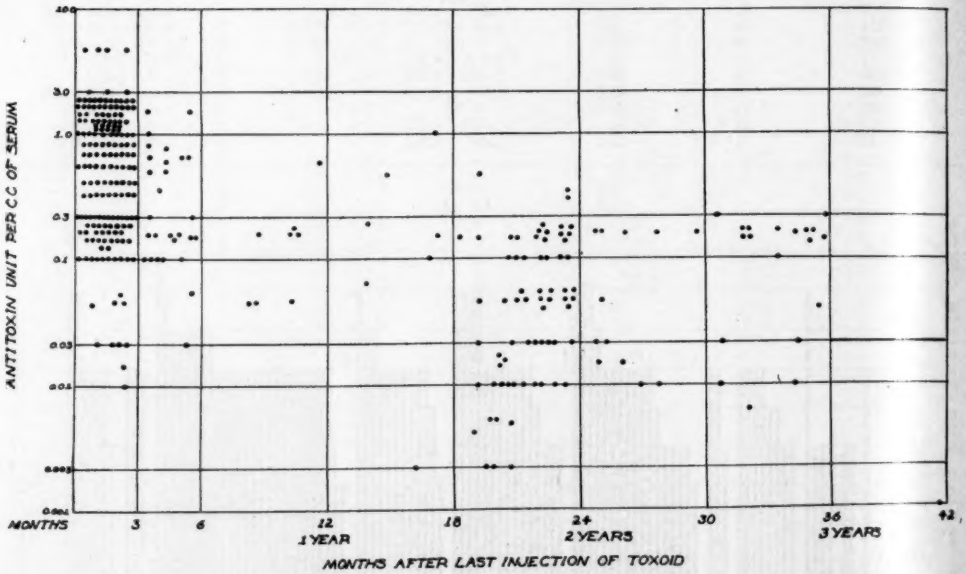

Chart 2.—Tetanus antitoxin titers (three injections of alum-precipitated combined diphtheria and tetanus toxoid with seven to twelve weeks between the first and third injections). This chart represents antitoxin titers before the recall injection. It includes many of the titers reported previously [1] as those taken within the first six months after immunization. Although not clearly indicated, no titers were obtained less than six weeks after completion of immunization. One patient may be represented by two dots, which indicates two titers taken at different intervals after completion of basic immunization. It can readily be seen that there was a downward trend in the titer level as the time following completion of immunization lengthened but that the majority of the subjects maintained a comparatively high level of antitoxin during the three year period.

be lower than those for the majority of the others.[8] Interesting also is the fact that the nine month titer was higher than that at three months, which indicates a slow response. It is entirely possible that the response to the recall injection was also slow. However, in comparison with all the others this child must be considered a poor producer of antitoxin.

8. Through a typographic error the titer of this subject was previously reported [1] as > 0.03 and < 0.01 nine months after basic immunity. This should have read > 0.03 and < 0.1, as indicated in table 1.

Of great interest is the level of antitoxin present prior to the recall injection. From chart 1 it will be seen that 48 per cent of the 100 subjects had 0.1 unit or more seventeen to thirty-six months (except for 1 at twelve months) after completion of basic immunization and 91 per cent had 0.01 unit or over. In other words, even without a stimulating injection at least 48 per cent of the 100 children can be considered protected against tetanus one and one-half to three years after basic immunization if 0.1 unit is accepted as a safe level and 91 per cent can be considered protected if 0.01 unit is accepted as protective.

If an attempt is made to correlate the level of the titer taken before the stimulation with that of one week later, it appears that there is no fixed relationship. There is, however, some tendency for subjects with low initial titers to have lower poststimulation titers. Most striking is the fact that the two lowest titers after the recall injection were obtained for patients who also had the two lowest titers prior

TABLE 3.—*Recall Data*

	Two Injections for Basic Immunity				
Subject No.	Weeks Between 1st and 2d Injection	Interval in Months Between Last Injection and Recall Titer	Initial Titer, Units per Cc. of Plasma	Interval in Days After Recall Injection and Titer	Recall Titer, Units per Cc. of Plasma
187	24	22	>0.01 <0.03	7	> 0.03 < 0.1
222	4	24	>0.03 <0.1	7	> 0.1 < 0.3
176	5	23	>0.03 <0.1	7	> 0.3 < 1.0
96	4	36	0.1	7	> 0.3 < 1.0
480	4	19	0.003	7	> 1.0 < 3.0
12	37 (0.5 and 0.5 cc.)	19	0.3	7	> 1.0 < 3.0
5	5 (0.5 and 1.0 cc.)	27	0.03	7	3.0
20	4 (0.6 and 1.0 cc.)	25	0.01	7	3.0
193	4	24	>0.1 <0.3	7	3.0
62	19	20	>0.1 <0.3	7	> 3.0 <10.0
131	10	23	>0.1 <0.3	7	> 3.0 <10.0
186	4	22	0.03	7	> 3.0 <10.0
204	4	21	0.1	7	> 3.0 <10.0
67	26	30	>0.1 <0.3	7	> 3.0 <10.0
355	4	22	>0.003 <0.01	10	> 3.0 <10.0
70	4	25	>0.03 <0.1	7	> 3.0 <10.0
174	5	23	0.1	7	>10.0 <30.0
243	4	24	>0.03 <0.1	7	>10.0 <30.0
175	5	23	>0.03 <0.1	7	30.0
21	27	21	>0.1 <0.3	7	>30.0 <60.0

to the injection. Analyzing this tendency further, we can proceed as follows: The greatest number of titers after the recall stimulation fall in the 3 to 10 unit group (51 per cent). There are 22 children with a titer above this level and 27 with a titer below it. Of the 22 above, only 1 had a titer of less than 0.03 unit just prior to recall. Of the 27 below the 3 to 10 unit level, there were 10 whose titer was less than 0.03 just prior to recall. No child failed to show a rise in titer one week after stimulation, the smallest being approximately a tenfold rise and the greatest over one thousand fold.

In table 3 are listed results for those children who received but two injections of basic immunization. The majority were given the injections at intervals of four or five weeks, but for some there were ten, nineteen, twenty-four, twenty-six, twenty-seven and thirty-seven weeks between injections. There are 20 children in this group; 2, or 10 per cent, had titers below 0.01 unit nineteen to twenty-five months after completion of basic immunization. The lowest titer (0.003 unit) rose to between 1 and 3 units a week later, and the next lowest (>0.003 <0.01 unit) rose to between 3 and 10 units ten days later. In this small group 4, or 20 per cent, had titers below 1 unit seven days after the stimulating dose, as compared

with 5 per cent in the larger group (100) receiving three injections for the basic immunization. Again, if 0.01 unit is considered as the protective level, then 45 per cent had that level or more at the time of the recall injection. If the lower level, of 0.01 unit, is protective, then 90 per cent fell in the protected group (i. e. results almost identical with those for the group receiving three injections chart 1). In some subjects the titer rose to extremely high levels, as there were 2 in the group with titers between 10 and 30 units; 1 had a titer of 30 units, and 1 a titer of between 30 and 60 units. However, the patients with but two injections comprise too small a group on which to base conclusions.

The great individual variation in antitoxin response is brought out in table 4, giving the figures for nine groups of siblings and one pair of twins. Each group received the same amount of toxoid with the same intervals between injections

TABLE 4.—*Recall Data on Siblings and Twins*

Subject No.	Weeks Between First and Last Injection	Months Between Last Injection and Recall	Initial Titer, Units per Cc. of Plasma	Days Between Titer and Injection	Titer, Units per Cc. After Stimulating Dose of 0.5 Cc. of Alum-Precipitated Tetanus Toxoid
116	8	24	0.01	7	> 1.0 < 3.0
48	8	24	0.03	7	>10.0 <30.0
57	11	23	>0.03 <0.1	7	>10.0 <30.0
58	11	23	>0.1 <0.3	7	>30.0 <60.0
168	9	21	>0.1 <0.3	7	> 3.0 <10.0
169	9	21	>0.1 <0.3	7	> 1.0 < 3.0
189	16	20	>0.03 <0.1	7	>10.0 <30.0
190	16	20	>0.1 <0.3	7	> 3.0 <10.0
280	8	23	0.01	7	> 3.0 <10.0
274	8	23	>0.06 <0.1	7	> 1.0 < 3.0
309	8	23	>0.03 <0.1	11	> 3.0 <10.0
310	8	23	0.03	11	>10.0 <30.0
315	19	20	0.1	7	> 3.0 <10.0
316	19	20	>0.03 <0.1	7	> 1.0 < 3.0
361	8	23	0.03	7	3.0
362	8	23	>0.03 <0.1	7	> 1.0 < 3.0
174*	5	23	0.1	7	>10.0 <30.0
175*	5	23	>0.03 <0.1	7	30.0
176*	5	23	>0.03 <0.1	7	> 0.3 < 1.0
Twins (double ovum)					
508	10	20	>0.003 <0.01	6	> 1.0 3.0
509	10	20	0.01	6	> 1.0 3.0

* These patients were given only two injections of 1 cc. each of alum-precipitated diphtheria and tetanus toxoid. All other patients received three injections of the same preparation.

and determination of titer. Here the only variations were in the subject and the age. Only one group gave identical titers before stimulation, and none gave either consistent or similar rises in titer after stimulation. The group of 3 children (subjects 174, 175 and 176) is especially interesting, with the initial titers close together and the poststimulation titers varying from between 0.3 and 1 unit to between 10 and 30 units.

The individual variation is also shown on chart 3 representing results of repeated determinations of titer for 3 members of the staff. This illustrates also that in these 3 persons the peak of the antitoxin response (after two injections of alum-precipitated tetanus toxoid) was obtained about three to eight weeks after the second injection. Thereafter it fell to lower but still significant levels five and six months later.

INTRADERMAL ADMINISTRATION OF TOXOID

Table 5 represents a small group for whom the stimulating dose of toxoid consisted of 0.1 cc. of plain tetanus toxoid given intradermally instead of 0.5 cc. of alum-precipitated toxoid given intramuscularly. While the number of subjects in

TABLE 5.—*Recall Data, Intradermal Injection of Toxoid*

Subject No.	Interval in Weeks Between First and Last Infection	Interval in Months Between Last Injection and Recall Titer	Antitoxin Titer	Interval in Days After Intradermal Injection of 0.1 Cc. of Plain Toxoid	Antitoxin Titer, Units per Cc. After Stimulation
13	8	34	0.01	7	1.0
17	8	35	>0.03 <0.1	8	>1.0 < 3.0
60	8	32	>0.1 <0.3	7	3.0
214	8	24	>0.03 <0.1	7	3.0
185	6*	26	>0.1 <0.3	4	3.0
61	8	31	0.01	7	>3.0 <10.0
209	8	25	>0.1 <0.3	7	>3.0 <10.0
195	26	20	>0.1 <0.3	7	>3.0 <10.0
90	76	14	>1.0 <3.0	7	>3.0 <10.0
41	36*	26	>0.03 <0.1	7	>3.0 <10.0
218	4*	26	>0.1 <0.3	7	>3.0 <10.0
584	14*	12	0.01	4	>0.03 < 0.1
				8	5.0
				21	5.0

* Received only two injections, the rest three.

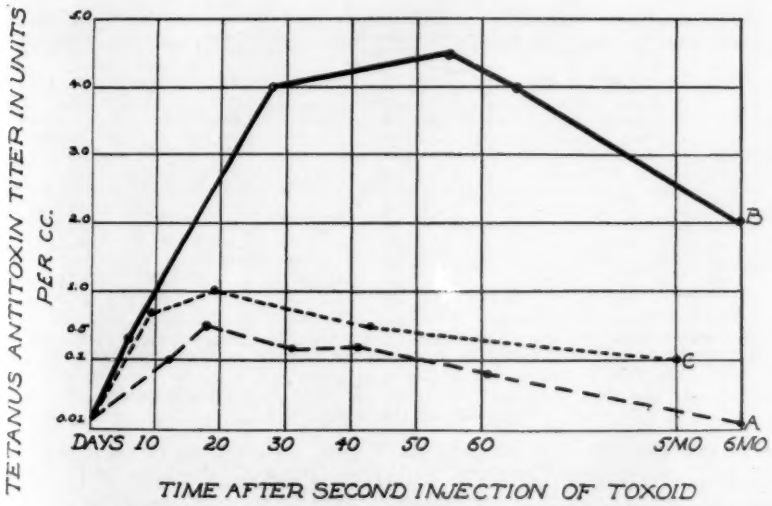

Chart 3.—Tetanus antitoxin titers of 3 subjects. A and B received two injections of 0.5 cc. of alum-precipitated tetanus toxoid three months apart; C received 1 cc. of alum-precipitated combined diphtheria and tetanus toxoid and three months later 0.5 cc. of alum-precipitated tetanus toxoid.

this phase of the study is small, it would seem significant that the injection of only 0.1 cc. intradermally caused a rapid rise in antitoxin titer to well above the basic levels. The lowest value was 1 unit, and 7 of the 12 subjects attained levels between 3.0 and 10.0 units at the end of a week. Intradermal immunization has been used with other agents, such as staphylococcus toxoid, diphtheria toxoid, scarlet fever toxin and typhoid vaccine. By this route a very small amount of antigen can be absorbed rapidly and perhaps with effectiveness equal to that of a large quantity given by a different route. One of the criticisms against this method has been the severity of the local reactions. We encountered more local reactions than we did in using the intramuscular route, but none were severe. Of the 12 subjects in the group 3 showed a local reaction consisting of an immediate urticarial wheal which became erythematous and was evident as a pigmented area one week later. One child had a questionable nonanaphylactic reaction (the mother reported

that "he did not feel well that evening"), but there was no evidence of local reaction at that time or one week later. Bigler [9] has reported use of the intradermal route in primary immunization. His study is not yet completed, and what titers have been determined have been considerably lower than those obtained by intramuscular injection. It is suggested that once basic immunization has been established the intradermal route might be used as a means of stimulation. It probably has no advantage over the intramuscular route except that it saves material and possibly there is less likelihood of a general anaphylactic reaction. However, in over 100 subjects who had received recall injections of alum-precipitated tetanus toxoid we did not encounter any reactions of the anaphylactic type. Our use of 0.5 cc. of the alum-precipitated toxoid as a stimulating dose was arbitrary. The combined tetanus and diphtheria toxoid might also have been used for recall injection, although the chance of reaction is probably greater with the diphtheria toxoid and the need of this fraction is probably less.

TABLE 6.—*Passive Immunization*

Patient	Days Between Injection and Titer	Units of Antitoxin	Titer, Units per Cc. of Plasma
C. J.	6	1,500	>0.03 <0.1
A. B.	8	1,500	>0.1 <0.3
W. B.	8	3,000	<0.001
G. F.	15	4,500	>0.003 <0.01
H. M.	15	3,000	>0.01 <0.03
E. P.	10	1,500	>0.1 <0.3
G. A.	7	1,500	0.1
W. P.	9	1,500	>0.03 <0.1
L. A.	7	1,500	>0.03 <0.1
E. H.	6	1,500	>0.03 <0.1
M. L.*	14	80,000	5.0
	19	.....	>1.0 <3.0
	28	.....	>0.3 <1.0

* This patient with tetanus was given 40,000 units of antitoxin intravenously and 40,000 units intramuscularly; he also received 1 cc. of fluid toxoid on entry to the hospital and on the eighth, nineteenth and twenty-eighth days after entry.

PASSIVE IMMUNIZATION

In table 6 are the titers of 10 patients [10] (not all children) taken six to fifteen days after administration of antitoxin (1,500 to 4,500 units) and of 1 patient with tetanus, who received a much larger dose. The protection afforded by the usual single dose of antitoxin is rarely adequate if it is assumed that 0.1 unit is the minimum protective level. Of 10 patients only 3 had a titer 0.1 unit or above. Four had values in the next lower group, that is between 0.03 and 0.1 unit, and 2 had titers below 0.01 unit. Bigler found somewhat higher levels than this in 64 children given a prophylactic dose of 1,500 units of antitoxin but noted a rapid fall after the first week to negligible amounts by three to four weeks. With the average incubation period of tetanus ranging between seven and fourteen days, not many of the patients in this group would appear to be adequately protected. A second or even a third dose is recommended for more certain protection but is rarely given. Probably the reason that tetanus does not develop more frequently after prophylactic administration of toxin-antitoxin is the surgical care of the wound which usually accompanies its administration and the absence of tetanus spores in the wound.

9. Bigler, J. A., and Werner, M.: Active Immunization Against Tetanus and Diphtheria in Infants and Children, J. A. M. A. **116**:2355 (May 24) 1941.

10. Through the cooperation of Dr. J. C. Geiger, Director of Public Health of San Francisco, and his staff many of these titers were obtained from patients entering the emergency hospital.

Even if the antitoxin levels were satisfactory one week after injection of a standard dose of antitoxin, there would still be failure to protect the many victims of minor injuries for which no medical advice is sought or which are considered by the physician too trivial to warrant the risk, expense and inconvenience of treatment with antitoxin.

That the city streets may still be considered as potential sources of tetanus infection in spite of the diminution in number of horse-drawn vehicles has been shown by Gilles.[11] As recently as 1936-1937 he found 14.2 per cent of random samples of dirt from the streets of Baltimore to contain toxic strains of Clostridium tetani.

COMBINED DIPHTHERIA AND TETANUS TOXOID, ALUMINUM HYDROXIDE ADSORBED

In the last year we have used an aluminum hydroxide–adsorbed combined diphtheria and tetanus toxoid. We previously had changed the interval between injections to two months instead of one. Table 7 shows the reports on the initial

TABLE 7.—*Three Injections of Combined Toxoid, Aluminum Hydroxide Adsorbed* *

Patient	Interval Between 1st and 2d Injection, Weeks	Interval Between 2d and 3d Injection, Weeks	Interval Between 1st and 3d Injection, Weeks	Interval Between Last Injection and Titer, Mo.	Antitoxin Titer
M. P.	9	8	17	1	>3.0 <10.0
M. P.	9	8	17	3	1.0
J. S.	10	10	20	1	>1.0 < 3.0
F. D.	9	10	19	1	1.0
M. F.	9	7	16	1	3.0
W. H.	8	9	17	3	>1.0 < 3.0
J. H.	8	10	18	3	1.0
S. H.	8	10	18	3	>1.0 < 3.0
D. J.	10	11	21	2	>0.3 < 1.0
J. M.	8	9	17	3	3.0
N. L.	9	9	18	3	>3.0 <10.0

* Aluminum hydroxide-adsorbed combined diphtheria and tetanus toxoid was supplied by the Cutter Laboratories.

titer of the first 11 patients given the aluminum hydroxide–adsorbed toxoid. In 750 patients given 1 to 3 injections of alum-precipitated combined toxoid there were three sterile abscesses [12] and several examples of nodule formation; all of these lesions gradually subsided without severe reaction. In 220 patients given one to three injections of aluminum hydroxide–adsorbed combined toxoid there has been no abscess formation and only 1 reported nodule formation. The local erythema appears to be about equal with the two preparations. It is our impression that both local reaction and nodule formation are in part dependent on the depth to which the needle is inserted and the degree of massage after injection. The deeper injections followed by thorough massage are less apt to give reactions.

COMMENT

As yet there is no way of testing antitoxin content except by animal titration of the patient's blood. Naturally this method requires too much time to be a practical test on which to base the need of a stimulating dose. Also, what of the cryptogenic

11. Gilles, E. C.: The Isolation of Tetanus Bacilli from Street Dust, J. A. M. A. **109:** 484 (Aug. 14) 1937.

12. Two of these were previously reported,[1] and their occurrence was felt to be due to the fact that the injections were given too superficially. The third was in a 1 year old infant and was very small, yielding only a few drops of sterile pus on aspiration.

infections, the splinters and the small wounds which constitute a common source of tetanus infection, especially in children? We favor a regular recall injection irrespective of injury and are of the opinion that a basic immunization with three injections of 1 cc. of a precipitated combined diphtheria and tetanus toxoid constitutes adequate protection against tetanus for the majority of persons if a stimulating dose of tetanus toxoid is given every two to three years and on receipt of injury. On the certificate of immunization given the patients in the clinic we have added the following notes:

To the Parent: Your child has received the recorded immunization. If he has received injections against whooping cough or tetanus (lockjaw), he should receive a boosting injection against each of these diseases not over two years later.

If at any time because of injury it is necessary to raise his immunity against lockjaw, show this card to the doctor caring for the injury.

To the Physician: If the above record shows that this patient has received basic immunization against tetanus (two injections [13] or more), we suggest, if possible, that in case of an injury calling for protection against tetanus he receive an injection of tetanus toxoid (plain or precipitated) instead of tetanus antitoxin. It should be given promptly (within twenty-four hours of the injury).

If precedent is needed for the omission of antitoxin, it is afforded by the Army and Navy routine, which calls for a boosting injection of toxoid every year and at the time of injury. Only in unusual cases—for example, when there has been excessive bleeding—is antitoxin given as well.

On the basis of our results all but 2 per cent of basically immunized children can be expected to elevate their titer to above 0.3 unit within one week if a stimulating dose of 0.5 cc. of toxoid is given at the time of the injury. No subject failed to show an appreciable rise one week after stimulation, and, as illustrated in chart 3, the indication is that the seven day level may not be the peak, especially for persons who respond slowly. The work of Strenge [14] also indicates that seven days may not be the height of the antitoxin titers.

SUMMARY

In all but 2 of 100 children given basic immunity seventeen to forty-two months previously by the use of three injections of 1 cc. of combined diphtheria and tetanus toxoid, alum precipitated, there was a satisfactory level of tetanus antitoxin obtained one week after a stimulating injection of toxoid. These 2 children showed at least a tenfold rise in antitoxin level, to over 0.01 and 0.03 U.S.P. unit respectively, which some consider sufficient for protection.

Even without a stimulating injection many of the infants and children in this study had presumptively protective levels up to three years after basic immunization.

Active immunization against tetanus is a more satisfactory procedure for children than is passive immunization.

University of California Hospital.

13. The insertion of "two injections" should not be construed as our advocating this as a routine practice. Rather it is our feeling that if a patient has been given but two injections he should still receive the recall toxoid rather than antitoxin at the time of injury. Basic immunization may be established by two injections, but we feel its adequacy is more certain if three injections are given.

14. Strenge, H. B.: Yale J. Biol. & Med. **12**:487, 1940.

Case Reports

DIAPHRAGMATIC HERNIA

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BALTIMORE
AND
CAPTAIN D. JAMES GREINER
MEDICAL CORPS, ARMY OF THE UNITED STATES

The occurrence of a true congenital diaphragmatic hernia of the right dome is sufficiently infrequent to warrant report of an additional case.

REPORT OF A CASE

T. H., a white boy, responded promptly to resuscitation and appeared perfectly normal at birth. At the end of the second week, the mother noticed the infant's respiratory rate seemed unusually rapid. He seemed normal in all other respects.

When T. H. was 7 weeks old, he was seen by one of us. The respiratory rate was greatly accelerated, and there was a pronounced retraction of the interspaces with each respiration. The conformity of the thoracic cage was disturbed by a definite bulging of the right anterior portion of the wall of the chest. The nail beds of the fingers and toes had a slightly cyanotic appearance. The trachea was deviated to the left. The heart was percussible to the left anterior axillary line. Auscultation revealed the heart sounds as being normal. There was a pronounced impairment of the normal resonance in the right anterior portion of the chest, with hyperresonance on the left. The breath sounds throughout the right side of the chest anteriorly were extremely distant, and there were heard numerous crepitant and subcrepitant rales. Posteriorly the breath sounds were absent. The remainder the examination on this occasion revealed nothing of any significance.

Roentgen examination at this time showed the heart and great vessels pushed to the left. There was also seen an area of increased density in the right lung extending from the fourth rib to the diaphragm and from the hilus to the outer zone of the lung. The density was practically the same as that of the heart shadow. The costophrenic angle was clear. The impression of the roentgenologist was that the area in the right side of the chest was probably a fluid-containing cyst or tumor of the lung (fig. 1).

Surgical consultation was sought after this report was received, and an exploratory tap was done. Air alone was obtained. Because of the age of the patient, it was deemed advisable to delay operative intervention until later.

The patient from this time until 5½ months of age did fairly well. He gained weight and seemed to experience no particular distress. Roentgen examinations made at approximately monthly intervals revealed no change from the condition shown on the original roentgenogram.

On Jan. 2, 1941, when 5½ months of age, T. H. was admitted to the University Hospital for surgical intervention. On the second day in the hospital, and, coincidentally, the day he was scheduled to be operated on, he became deeply cyanotic and had an elevation of temperature to 104 F. Examination revealed the presence of lobar pneumonia in the upper lobe of the left lung. Pneumococci were cultured from material from the throat, but the type was not determined. The temperature returned to normal in twenty-four hours after the administration of sulfapyridine. On the seventh day the patient was doing well, and he was then discharged, as it was thought advisable to defer operation for several weeks.

While at home the patient was well for several days and then an infection of the upper respiratory tract developed which resulted in a disseminated pneumonia. He was readmitted to the University Hospital on February 13.

From the Departments of Pediatrics and Pathology of the University of Maryland School of Medicine and the University Hospital.

Examination at this time revealed a deeply cyanotic and dyspneic infant. Numerous rales were heard through the pulmonary fields. The heart sounds were rapid and of a poor quality. The extremities were cold. The temperature was 103.4 F. The leukocytes were moderately increased, and the stained smear showed a predominance of granulocytes. Sulfapyridine was administered. The temperature continued to be elevated, ranging from 102 to 104 F. daily. Physical examination during the last two days of life showed that breath sounds throughout the right side of the chest were completely absent. On February 16, three days after his readmission, the infant died. The clinical diagnosis was bronchopneumonia and congenital cyst of the right lung.

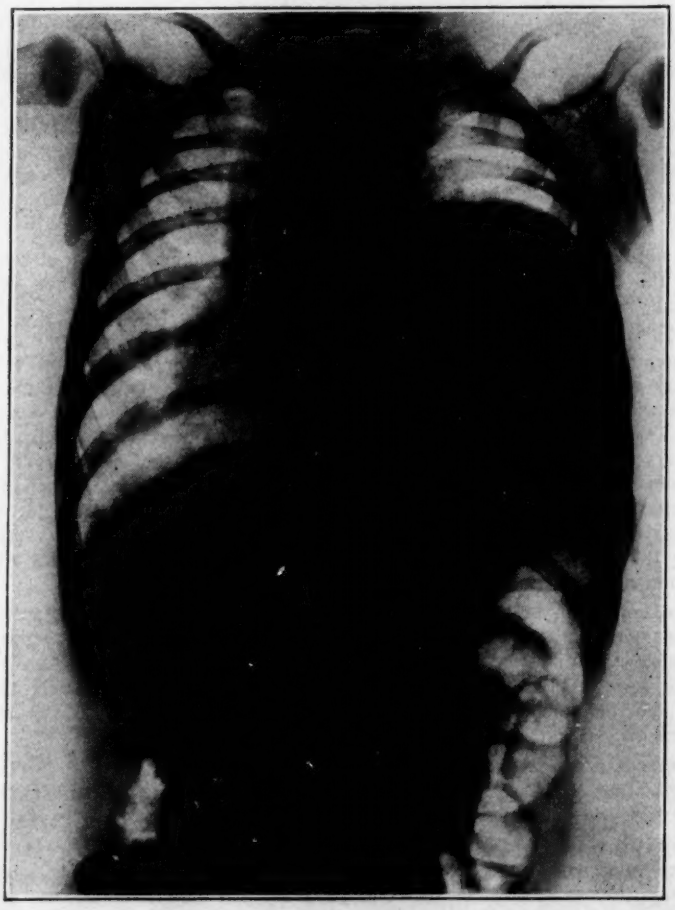

Fig. 1.—Roentgenogram of the chest, showing the displacement of the heart and great vessels and the area of increased density in the right lung which proved to be liver.

Autopsy revealed bronchopneumonia of the left lung. The right thoracic cavity showed rudimentary development of the right lung. The organ was adherent to and compressed by a rounded solid mass which rendered it completely atelectatic. On examination, the mass was noted to be a portion of the right lobe of the liver and the gallbladder covered by a thin fibrous membrane which could be reflected in a glovelike manner after the diaphragm had been freed. This membrane was a defective portion of the diaphragm which formed a hernia sac with an opening measuring 4 cm. in diameter (fig. 2). Grossly, no muscle was seen in the membranous sac of the diaphragm. Microscopically, there was a pronounced thinning of the diaphragm at the site of herniation and the musculature was represented only by a few scattered muscle fibers. There was no evidence of inflammatory change (fig. 3). The other organs examined at autopsy showed no unusual lesions.

COMMENT

Developmentally and anatomically the diaphragm is an organ which has many potential points for herniation. The normal diaphragm contains three large and several smaller openings. The aorta, esophagus and vena cava pass through the large openings. Through the smaller openings pass the splanchnic nerves, greater and lesser, and the vena azygos minor.

In the complex embryologic development of the diaphragm, there are seen additional sites for the development of hernia. The complete diaphragm arises from several sources and is the result of fusion of these various components. The ventral portion is derived from the septum transversum; the lateral portions develop from both the pleuroperitoneal membranes and derivatives of the body wall; the dorsal median portion is derived from the dorsal mesentery, and finally the muscle fibers are derivatives of the third and fourth cervical myotomes. There

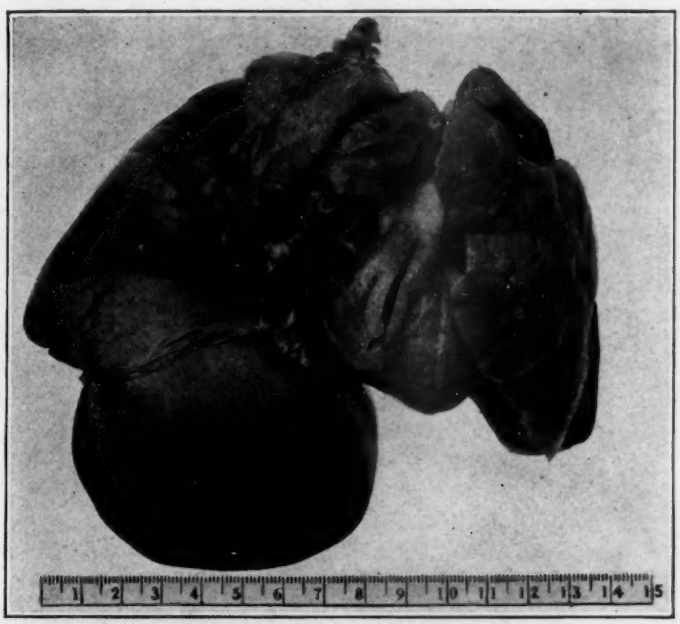

Fig. 2.—Reflection of the hernial sac over the right lobe of the liver.

are opportunities for imperfect fusion of these various portions in the formation of the structure. A small opening sometimes remains between the pleural and the peritoneal cavity in the lumbar region. This is the hiatus pleuroperitonealis, or foramen of Bochdalek. Failure of proper fusion of the central and sternal fibers at either side of the sternum will result in an anterior defect known as the foramen of Morgagni. Occasionally a portion or all of one side of the diaphragm fails to develop.

The most frequent sites of diaphragmatic hernia are through the foramen of Bochdalek, through the esophageal hiatus, through the foramen of Morgagni, through the dome of the diaphragm and through the gap left by the absence of the hemidiaphragm. Essentially the hernias are classified into true or false according to the presence or absence of a hernial sac. A further subdivision into congenital and acquired hernias is given by most authors.

Congenital hernia is less common than the acquired variety. Riverius[1] is credited with the first recognition of the congenital type, in a case which he reported in 1689. Hedblom,[2] in a review of 1,408 cases which did not include esophageal hiatus hernias, found 355 of the congenital variety, or an incidence of 1 in 4. Hernia of any type is more common on the left side, and of the congenital variety

Fig. 3.—Photomicrograph, showing only a few muscle fibers at the site of herniation and no evidence of any inflammatory change.

it may be said that it occurs more frequently on the left side than on the right, in the ratio of 12 to 1. Greenwald and Steiner[3] in a series of 82 congenital

1. Riverius, L.: Opera medica universa, London, J. H. Huguetan, 1690.
2. Hedblom, C. A.: Diaphragmatic Hernia, Ann. Int. Med. **8**:156-176 (Aug.) 1934.
3. Greenwald, H. M., and Steiner, M.: Diaphragmatic Hernia in Infancy and in Childhood, Am. J. Dis. Child. **38**:361-372 (Aug.) 1929.

hernias in children up to 10 years of age, found 16 on the right side; of these 10 were false, 3 true and 3 of undetermined nature. Of the 3 congenital right-sided hernias, none contained liver. Jenkinson and Roberts [4] in a series of 85 congenital hernias found only 2 on the right side. In neither of these did the liver form the contents of the hernial sac. Kerr and Steinberg [5] stated that true congenital diaphragmatic hernia is an uncommon condition and that herniation involving the right dome is very rare. They reported 3 cases, in none of which was the liver involved. Unger and Poppel [6] cited Lupman to the effect that 87 per cent of congenital hernias are false in that they are without a sac; that 13 per cent have a definite sac and are true hernias, and that hernias of the congenital type, true or false, occur usually on the left side.

In the cases of true congenital hernia of the right side, it will be noted that the liver was not involved. However, in the literature Hedblom [2] and Harrington and Kirklin [7] reported that in the rare cases of hernia through the right arch of the diaphragm, a portion of the liver usually projected through the breach. Barney and Evans [8] reported 2 cases, in 1 of which a true congenital hernia contained the liver in the thin-walled sac. Lilienthal [9] reported a true congenital hernia occurring in an adult, with the liver protruding in the sac.

It has been stated [10] that the cause of diaphragmatic hernia is often obscure, its pathologic anatomy diversified and its clinical manifestations manifold. The chief etiologic factor, particularly in the congenital type, is usually a failure of fusion of the various component parts of the embryologic diaphragm.[11] In addition, partial weakness in the structure of the diaphragm, which may be the result of a local lesion or of increased intra-abdominal pressure, must be mentioned.[12] Those hernias which occur through the dome of the diaphragm are believed due to an excessive degeneration of the muscle in the formation of the central tendon or to a local pathologic condition as the result of interference with the circulation or innervation. The part which increased intra-abdominal pressure plays is probably important. Bowen [13] stated that it is interesting to note that in the fetus the increased intra-abdominal pressure due to the rapid increase in the size of the liver and in the length of the midgut produces a physiologic umbilical hernia. Any existing embryologic defects in the diaphragm would permit herniation of viscera through the defect in the presence of this increased intra-abdominal pressure. The possible reason for the rarity of congenital hernia on the right side as

4. Jenkinson, E. L., and Roberts, E. W.: Lesions of Diaphragm, Am. J. Roentgenol. **38**:584-591 (Oct.) 1937.

5. Kerr, H. D., and Steinberg, S. S.: Right-Sided Diaphragmatic Hernia with Report of Three Cases, Am. J. Roentgenol. **34**:735-739 (Dec.) 1935.

6. Unger, A. S., and Poppel, M. H.: Diaphragmatic Hernia, Am. J. Roentgenol. **37**: 472-478 (April) 1937.

7. Harrington, S. W., and Kirklin, B. R.: Clinical and Roentgenologic Manifestations and Surgical Treatment of Diaphragmatic Hernia, with Review of One Hundred and Thirty-One Cases, Radiology **30**:147-156 (Feb.) 1938.

8. Barney, W. R., and Evans, E. H.: Congenital Diaphragmatic Hernia, Arch. Pediat. **41**:720-723 (Oct.) 1924.

9. Lilienthal, H.: Diaphragmatic Hernia of Liver, S. Clin. North America **11**:475-481 (June) 1931.

10. Hedblom, C. A.: Diaphragmatic Hernia: A Study of Three Hundred and Seventy-Eight Cases in Which Operation Was Performed, J. A. M. A. **85**:947-953 (Sept. 26) 1925.

11. Donovan, E. J.: Congenital Diaphragmatic Hernia, Ann. Surg. **108**:374-388 (Sept.) 1938.

12. Friedman, M., and Ehrlich, L. H.: Diaphragmatic Hernia on Right Side, Am. J. Dis. Child. **50**:443-453 (Aug.) 1935.

13. Bowen, A.: Diaphragmatic Hernia: Review of Literature, Am. J. Surg. **39**:4-11 (Jan.) 1938.

compared with the left was mentioned by Bowen, namely that the closure of the right leaf of the diaphragm takes place before that of the left leaf. Others [14] in commenting on this same point have listed the generally accepted reasons as threefold, namely: The diaphragm is supported by the mass of the liver; the right crus is longer and thicker, and there are two fibrous bands on the right side.

The fact that both the congenital and the acquired type of hernia may or may not have a sac sometimes leads to difficulty in proper classification in any given case. Hernias of the congenital type usually show evidence of long standing. This is present in the structures affected by the hernia. The evidences of herniation long before birth [15] are the undeveloped condition of the lung and if the malformation is on the right side the molding of the liver, embedding the round ligament within it. Occasionally the kidney is displaced upward.

Diaphragmatic hernia is a lesion which may cause a variety of clinical symptoms. The traumatic type may be attended by acute symptoms, while the nontraumatic type, either congenital or acquired, may produce long-standing vague complaints or no evidence of symptoms referable to the lesion and the diagnosis may be made only during the course of an examination for some other condition. It is apparently possible for extensive defects in the diaphragm, amounting even to complete absence of half of the organ, to exist without causing any disability to the person.[16] With the congenital variety the symptoms which do result are often respiratory rather than related to the alimentary tract, because of the displacement of the mediastinum and the compression or maldevelopment of the lung. The chief symptoms in infants and children include dyspnea, cyanosis, asymmetry of the chest, diminished excursion of the chest wall, tympany or dulness on percussion, disturbed or absent breath sounds, displacement of the heart, various respiratory difficulties and peculiar weak cry.[17] Truesdale [18] mentioned both respiratory and alimentary symptoms in infancy and childhood, characterized by dysphagia, pyloric obstruction, vomiting, constipation, dehydration and cough. This type of symptom complex would be more likely to occur in left-sided hernias in which a small or large portion of the gastrointestinal tract is often the contents of the hernia. Hernias through the right dome with little or no portion of the intestine in the thorax may cause only vague respiratory symptoms.

The diagnosis of diaphragmatic hernia may be difficult. The diagnosis is made much more frequently now than before the advent of roentgen examination. The incidence, however, is no greater now than twenty years ago; at that time it was considered an uncommon condition, and recognition in life was rare.[7] Its appearance in children is still considered rare, and apparently this is more indicative of the difficulties of recognition than of the actual rarity of its occurrence.[19] In practically all of the cases previous to roentgen examination diagnosis was made either at operation or at the autopsy table. This was particularly true of children. Even

14. Meyer, K. A.; Hoffman, S. J., and Amtman, J. K.: Diaphragmatic Hernia in Newborn: Review of Literature and Report of Case, Am. J. Dis. Child. **56**:600-607 (Sept.) 1938.

15. Liebow, A. S., and Miller, H. C.: Congenital Defects in Diaphragm, Am. J. Path. **16**: 707-738 (Nov.) 1940.

16. LeWald, L. T.: Roentgenological Diagnosis of Diaphragmatic Hernia, Am. J. Roentgenol. **20**:423-430 (Nov.) 1928.

17. (*a*) Marks, J. H.: Diaphragmatic Hernia and Associated Conditions, Am. J. Roentgenol. **37**:613-632 (May) 1937. (*b*) Greenwald and Steiner.[3] Meyer, Hoffman and Amtman.[14]

18. Truesdale, P. E.: Traumatic Rupture as Sequence to Congenital Hernia of Diaphragm with Experimental Study of Its Mechanism and Effects of Phrenicotomy, Ann. Surg. **90**: 654-668 (Oct.) 1929.

19. Truesdale, P. E.: Diaphragmatic Hernia in Child, Aged One Year, J. A. M. A. **96**:847-848 (March 14) 1931.

after roentgen examinations were available, many diaphragmatic hernias were unrecognized until operation or necropsy. Vannesson [20] in France reported 303 cases, in 165 of which diagnosis was made at autopsy and in 90 by roentgen study.

The herniated viscera may include anything except the rectum, genitalia and urinary bladder.[20] Naturally the malformations in which stomach or intestine forms the whole or a part of the herniated tissue offer the least difficulty in diagnosis. Even these, however, if of an intermittent type may give no indication of their presence on roentgen examination.

The hernias on the right side may offer more difficulty in diagnosis than those on the left. This is true even with roentgen examination of the patient. In childhood the liver is a comparatively large organ, and if the hernia is small it may be hidden by the shadow of the liver. Diagnosis is particularly difficult in the few cases in which the hernia includes only a portion of the liver.[17a] The mass, even if visualized by the roentgen rays, is interpreted as a local collection of fluid or pus or as a solid neoplastic growth.

CONCLUSION

A case is reported of the rare type of true congenital diaphragmatic hernia on the right side with a portion of the liver as the only content of the hernial sac. The condition had existed since early fetal life. This was evident by the malformation or molding of the right lobe of the liver, which projected into the hernial sac, and the adherent maldeveloped, or fetal, right lung, which was closely associated with the sac. The case was typical of this type of lesion. The symptoms were almost entirely respiratory, appeared within two weeks after birth and varied in type and intensity until the patient's death, at the age of 6 months.

5901 York Road.

20. Vannesson, A.: Contributión à l'étude des hernies diaphragmatiques congénitales chez le nouveau-né, Thesis, Paris, no. 388, 1912.

UNUSUAL OSSEOUS DISEASE WITH NEUROLOGIC CHANGES

REPORT OF TWO CASES

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AND
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The purpose of this report is to call attention to 2 unusual yet similar cases in which bizarre osseous changes and hyperreflexia were the outstanding features. We have been unable to find similar cases either in the literature or by consultation with persons versed in pathology of the bone. It is hoped that a presentation of the cases will call to light others and add to the understanding of this condition.

REPORT OF CASES

CASE 1.—M. M. (fig. 1 *A*) was admitted to the medical service in January 1940, at the age of 4 years and 10 months, because of a peculiar waddling gait, easy fatigability and failure to gain in weight. She was referred from the orthopedic clinic, where she was first seen six months previously. Examination at that time revealed a thin, underweight child who walked with a mild right abductor and calcaneus limp, with a fairly broad base. Two months later, she was again seen in the orthopedic clinic, at which time muscular weakness of the lower extremities was noted and muscular dystrophy suspected. Because she presented a diagnostic problem, she was admitted to the hospital for study.

The family history was noncontributory. One sibling, aged 6 years, was living and well. The birth and neonatal history were normal. She had chickenpox and measles in infancy and pertussis at the age of 2½ years. Since then, the mother said, the child had had an extremely poor appetite. There were no other symptoms relating to the gastrointestinal tract and no history of pica. Although the failure to gain in weight was an outstanding feature, her development in other respects appeared normal. She sat alone at 6 months and walked at 13 months; dentition was normal. Her intellectual development appeared satisfactory. Shortly after the child began to walk, her mother noticed a waddling gait. This had persisted, with little change. The child was not able to run, but she could walk up stairs with great effort. She was able to get up from the floor without climbing up on her thighs. She tired readily.

Physical examination on admission, at the age of 4 years and 10 months, revealed a delicate-appearing child, fully cooperative. She weighed 27 pounds (12.2 Kg.) and was 42 inches (107 cm.) tall; her pulse rate was 90 and her blood pressure 88 systolic and 56 diastolic. She was well proportioned. No muscular fibrillation or twitchings were noted. She walked with a straight leg, wide base, waddling gait. Her muscles appeared to be poorly developed generally, yet careful examination of them revealed surprisingly good strength. There were no contractures; no irregularities or prominences of the long bones were felt. Neurologic examination revealed generalized hyperactive deep tendon reflexes. Ankle clonus was elicited on a few occasions. The plantar reflexes were normal. The rest of the physical examination, including examination of the eyes, ears, nose and throat, teeth, heart, lungs, abdomen and genitalia, revealed normal conditions.

The patient was in the hospital for seven weeks, during which time numerous studies were carried out.

Roentgenograms of the long bones showed alterations in the architecture and density in the midportions of all the long bones, with fusiform swelling; this was characterized by areas of relatively increased density and mottled areas of decreased density. There was generalized poor mineralization, with slight coxa valga deformity of the hips. Roentgenograms of the skull showed no abnormalities. The bone age was within normal limits.

From the Department of Pediatrics, Harvard Medical School, and The Children's Hospital.

Repeated examinations of the urine gave normal results. The results of a dilution and concentration test of renal function were also normal. A test of the urine for Bence Jones protein revealed none. Creatinine excretion was 180 mg. and creatine excretion 44 mg. per

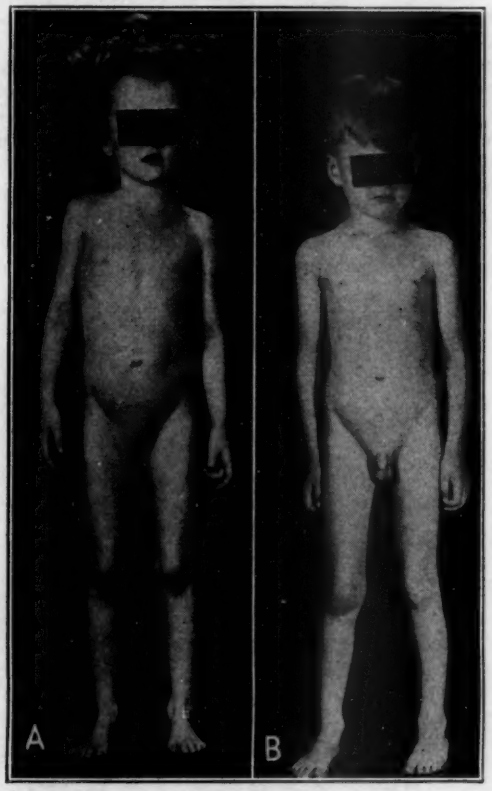

Fig. 1.—*A*, M. M. (case 1); *B*, J. B. (case 2).

Fig. 2.—Roentgenogram of long bones of M. M. (case 1).

hundred cubic centimeters in a twenty-four collection of urine. Examination of the blood on admission showed: red cells, 4,220,000; white cells, 6,800, and hemoglobin content 83 per cent. The blood smear appeared normal. The tuberculin test with a dilution of 1:100 produced a negative reaction. The response of the blood to a Hinton test was negative.

The spinal fluid was examined and found to be clear, with normal sugar content and a negative Pandy reaction. The colloidal gold curve was normal, as was the result of a Hinton test of the spinal fluid. Bacteriologic studies, including agglutination tests of the blood for Bacillus abortus and Bacillus typhosus, gave negative results. Chemical examinations of the serum revealed: calcium, 9.9 mg. per hundred cubic centimeters; phosphorus, 4.5 mg., and phosphatase, 3.7 Bodansky units. The nonprotein nitrogen content was 34 mg. and the serum protein 7.7 Gm. per hundred cubic centimeters. Because of the state of malnutrition and failure to gain, a series of gastrointestinal tests were carried out, as well as a test of absorption of vitamin A; the results of these tests were normal. On examination the stools also appeared normal. A test dose of 0.025 mg. of prostigmine methylsulfate was given subcutaneously, and no observable change was noticed in muscle strength. The patient was seen by the psychologist, who found her intellectually competent, with an intelligence quotient of 113. A biopsy of bone and muscle was performed.[1] No evidence of an inflammatory process was found; there were an increase in density of cortical bone and minimal evidence of bone resorption. As shown in the accompanying photograph, some atrophy of the skeletal muscles

Fig. 3.—Photomicrograph of a section of bone from the left tibia of M. M. (case 1), showing increased density of cortical bone and minimal evidences of resorption.

was noted. The site of the biopsy specimen was the left tibia, where the lesion was most severe, as predetermined by roentgen examination.

In the one and one-half years since discharge from the hospital, the patient has been seen at frequent intervals. Her gait is still as described previously; she is seriously undernourished, weighing 29½ pounds (13.4 Kg.) at 6¼ years of age. Her most recently determined blood calcium level was 8.6 mg. per hundred cubic centimeters and the phosphatase activity 8 Bodansky units. Repeat roentgenograms of the long bones showed the change in the shafts to be more pronounced, which suggests that there may be a continuation of the process. The deep tendon reflexes at present are not nearly so active as when she was first admitted to the hospital, at the age of 4 years and 10 months.

CASE 2.—J. B. (fig. 1 *B*), a 4 year 11 month old white boy, an only child, was admitted to the neurologic service of the Children's Hospital in June 1942, because of a peculiar gait of about eighteen months' duration. The family history contained no record of muscular

1. Drs. William T. Green and Sidney Farber made this examination.

dystrophies. The father had a fracture of a thoracic vertebra, shown by roentgenograms. The birth and neonatal history were normal. He sat up at 7 months but did not walk until he was over 2 years old. Dentition was normal. He had had no severe or acute illnesses.

Shortly after an accident in which he fell from a tricycle at the age of 3½ years, his parents noticed a limp, and since then he has not walked normally. He has been unable to run. It was also noticed that in kindergarten he did not join in games with the other children, that he always clung to the rail in walking up stairs and that he tired easily. At about the same time, his mother noticed that he was beginning to have a poor appetite, which has become worse. He was seen in the orthopedic clinic at the age of 4 years and 2 months, when his gait was described as one of slapping his feet down. Extremely hyperactive reflexes and unsustained ankle clonus were noted. Examination of muscle strength showed no specific weakness. Because of persistence of symptoms and the observation of fusiform swellings of the femurs on palpation, he was admitted to the hospital for further study.

Physical examination showed a well developed and well nourished solemn boy in apparently good health. His height was 45 inches (114 cm.); his weight, 39 pounds (17.7 Kg.), and his blood pressure, 98 systolic and 50 diastolic. The gait was characterized by a wide base, legs kept almost straight at the knees, with a tendency to slap his feet down. When asked to run, he merely walked fast. He was able to stand on his toes and when asked to run on them did fairly well for a few steps. All deep tendon reflexes were extremely hyperactive, and there was a sustained bilateral ankle clonus, elicited more easily after exercise. Plantar reflexes were normal, but Hoffman digital reflexes were elicited on occasion. No specific

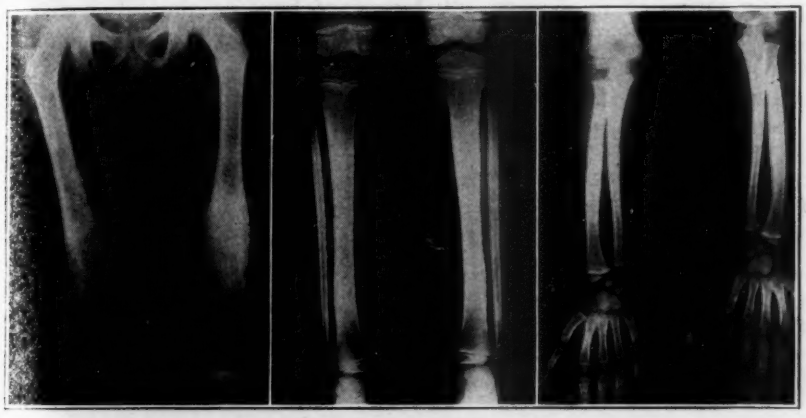

Fig. 4.—Roentgenograms of long bones of J. B. (case 2).

muscular weakness was detected. He tired more easily than normal. There were no sensory changes. Fusiform swellings were palpable at the lower end of both femurs, about 1 inch (2.5 cm.) above the knee. They were neither tender nor hot. The results of the rest of the examination, including study of the eyes, ears, nose, throat, teeth, heart, lungs, abdomen and genitalia, were normal.

Roentgenograms revealed changes in all the long bones and in the skull. In each femur, beginning about 1 inch (2.5 cm.) proximal to the epiphysis and extending about 4 inches (10 cm.) up the shaft, was a smooth fusiform dilatation of the shaft. The bone in this area was of generally increased density, but there were scattered areas of decreased density. The rest of the shaft was of normal density. There was a valgus deformity of the head of each femur. The tibias and fibulas showed an abnormal area of irregularly thickened cortex at each end of the diaphysis. A similar lesion involved the entire middle part of the shaft of each of the bones of the arm. In the femurs it was also noted that there was a little periosteal reaction over the swellings. The bones at the base of the skull showed a fairly pronounced increase in density. The bony contours, including the foramen magnum, were essentially normal. In the pelvis there was a small, rounded shadow appearing to be produced by bone and demonstrated by intravenous pyelograms to be cast by an object outside the genito-urinary tract.

Laboratory Data.—The urine was normal. Examination of the blood showed: hemoglobin content, 11 Gm.; red cells, 5,400,000, and white cells, 12,700, of which 51 per cent were polymorphonuclear leukocytes, 47 per cent lymphocytes and 2 per cent monocytes. No abnormalities were noted on a smear preparation. The spinal fluid was normal, with a total protein

content of 15 mg. per hundred cubic centimeters. The Hinton reactions of the blood and spinal fluid were negative. The tuberculin patch test gave a negative reaction. The calcium content of the blood was 9.8 mg. per hundred cubic centimeters; the phosphorus content, 4.55 mg., and the phosphatase activity, 6.45 Bodansky units. The serum protein level was 6.7 Gm. per hundred cubic centimeters, and the blood cholesterol level was 160 mg. The plasma contained normal amounts of vitamin A and carotenoids. The urinary excretion of creatinine in twenty-four hours was 288 mg. per hundred cubic centimeters, and of creatine, 78 mg. per hundred cubic centimeters.

Permission to take a specimen of bone for biopsy has been refused up to the time of writing this report.

SUMMARY AND CONCLUSION

Two cases have been presented in which there were several outstanding features. Both children had a peculiar gait, which was characterized by a straight leg, a wide base and a calcaneus limp; neither child could run. Ankle clonus and hyperreflexia were present in both children. One child showed extreme anorexia, with emaciation; the other showed anorexia only. Both children fatigued easily. Roentgenograms of the long bones were similar, showing symmetric areas of increased density and dilatation of the bony shaft, with scattered areas of diminished density involving all the long bones. The base of the skull in 1 case (J. B.) was greatly increased in density. A biopsy of bone in the other case showed concentration of organic matrix and minimal evidence of bone resorption. There was no evidence of an inflammatory process.

In view of so many findings in common in 2 cases with such bizarre pictures, it would seem reasonable to suppose that in both there is the same underlying disease process.

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IDIOSYNCRASY TO MERCURY PREPARATIONS IN CHILDHOOD

REPORT OF TWO CASES OF REACTIONS TO 5 PER CENT AMMONIATED MERCURY OINTMENT AND MERCURY BICHLORIDE SOLUTION (1:4,000)

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The use of mercury preparations of various types in the treatment of disorders in childhood has been widespread for many generations. The value of mercury is beyond question, and the fact that few reports appear in the literature concerning idiosyncrasy to, or poisonings caused by, the local application of preparations containing it attests to the relatively safe character of such preparations. It has been estimated that in the United States at least one million packages of ammoniated mercury ointment are sold annually. This does not include the amounts of other commonly used ointments and lotions of mercury prescribed by members of the medical profession.

Mercury-containing preparations applied locally may cause reactions characterized by varying degrees of local irritation. The mildest reaction is limited to the area of application and consists simply of a mild erythema. In severe reactions, the area of erythema may spread to cover the entire body and may at the onset resemble measles or scarlet fever. The condition is frequently diagnosed as one of these diseases unless the history of the use of mercury is obtained. The original erythema may increase in intensity until the skin becomes severely indurated. Bleb formation may occur, and blebs as large as an adult fist may appear. Such a reaction may be accompanied by edema of the extremities and generalized lymphadenopathy. As the erythema subsides, the skin may blister and crack and then desquamate in sheets. Accompanying the cutaneous manifestations there may be high fever and severe prostration, and occasionally delirium, cyanosis and marked toxicity. No deaths from mercury preparations applied locally to the unbroken skin have been reported.

The reactions caused by a locally applied preparation of mercury are a true idiosyncrasy and not a poisoning. Some of the mercury is absorbed, but the quantity is so minute as to be incapable of causing damage to the internal organs. Gibbs, Shank, Pond and Hansmann[1] in a series of experiments performed on medical students showed that the daily application of 1 Gm. of a 10 per cent ammoniated mercury ointment, thoroughly rubbed into the skin, resulted in the excretion in the urine and feces of approximately 1 part in 3,800 parts of the mercury applied. By comparison 1 grain (0.065 Gm.) of mild mercurous chloride taken by mouth would require a hundred months to be excreted at this rate. When 2 per cent ammoniated mercury ointment was used, only traces of mercury appeared in the excreta. These authors concluded that the continued application of mercury ointment to the unbroken skin is not likely to cause poisoning.

From the Department of Pediatrics of the Brooklyn Jewish Hospital.

1. Gibbs, O. S.; Shank, R.; Pond, H., and Hansmann, G. H.: Absorption of Externally Applied Ammoniated Mercury, Arch. Dermat. & Syph. **44**:862-867 (Nov.) 1941.

Maloff,[2] in his study of the mercury ointments, stated the belief that the rarity of toxic effects from ammoniated mercury was accounted for by its poor absorption and that this was due to its being a complex insoluble mercury compound (NH_2HgCl), in contrast to the better absorbed metallic mercury mixture found in the U. S. P. mild and strong mercurial ointments (blue and gray ointments).

The first cases of idiosyncrasy to ammoniated mercury ointment recorded in the literature were reported by Deakin.[3] The patients were adults, and 7.5 per cent preparations of ammoniated mercury ointment were used. In both reactions developed within two days after application of the drug. Green [4] and Alexander and Mendel [5] reported 1 case each; in these cases also the idiosyncrasy appeared in an adult. The ointments involved were of 10 per cent and 5 per cent concentrations.

The earliest cases of idiosyncrasy to mercury ointments in children were reported by Harper.[6] His first patient was 20 months old. One day after application of the 10 per cent ointment a papulovesicular eruption on a thickened erythematous base developed, which spread to cover the entire body except the scalp. The second patient was 16 months old. A 10 per cent ammoniated mercury ointment was used for five days, after which a macular eruption appeared.

Reported Cases of Idiosyncrasy to Ammoniated Mercury Ointment

Year	Author	Age of Patient	Mercury Content of Ointment, Percentage	Time Used, Days
1883	Deakin [3]	Adult	7½	2
	Deakin [3]	Adult	7½	2
1884	Green [4]	Adult	10	1
1923	Alexander and Mendel [5]	Adult	5	?
1934	Harper [6]	20 months	10	1
	Harper [6]	16 months	10	5
1941	Bass [7]	6 years	10	8
	Bass [7]	4 years	1	6
	Bass [7]	6 years	5	7
	Bass [7]	4 months	3	7
	Bass [7]	15 years	?	1
1942	Wilbar [8]	18 months	15	7
1942	Gibel and Kramer	22 months	5	11

Bass [7] reported 5 cases of idiosyncrasy to ammoniated mercury ointments. The first patient was 6 years old; the rash appeared after eight days of application of the 10 per cent ointment. The second patient, 4 years of age, had an eruption after six days of application of a 1 per cent ointment. This same patient had a 5 per cent ointment applied fourteen months after the original application, and again a severe reaction developed. Mild mercurous chloride also was used by this patient, and a morbilliform eruption developed. In the third case reported a rash developed after seven days of application of a 5 per cent ointment; the patient was 6 years old. It is interesting to note that yellow mercuric oxide

2. Maloff, G.: Ueber die Resorption des Quecksilbers nach Applikation der weissen Präzipitätsalbe auf die Haut, Deutsche med. Wchnschr. **54**:1381 (Aug. 17) 1928.

3. Deakin, S.: Unusual Symptoms Following Applications of Unguentum Hydrargyri Ammoniati, Brit. M. J. **2**:1281-1282 (Dec. 29) 1883.

4. Green, W. E.: Unusual Symptoms Following the Use of Unguentum Hydrargyri Ammoniati, Brit. M. J. **1**:853-854 (May 3) 1884.

5. Alexander, A., and Mendel, K.: Chronische Quecksilbervergiftung durch langdauernden Gebrauch einer Sommersprossensalbe, Deutsche med. Wchnschr. **49**:1021-1022 (Aug. 3) 1923.

6. Harper, P.: Idiosyncrasy to Ammoniated Mercury Ointment: Report of Two Cases, J. Pediat. **5**:794-799 (Dec.) 1934.

7. Bass, M. H.: Idiosyncrasy to Ammoniated Mercury Ointment in Childhood, Urol. & Cutan. Rev. **45**:78-81 (Feb.) 1941.

The patient in case 1. The intense erythema can be seen (compare with hands holding child). Note the large bullae on the fingers, buttocks, back and lower extremities. A large ruptured bullae can be seen on the left elbow.

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was used during several attacks of acute catarrhal conjunctivitis, without reaction. In his fourth case the idiosyncrasy appeared in a patient 4 months old who received two daily applications of a 3 per cent ointment; a rash developed after seven days. In the last case a reaction occurred in a 15 year old girl who had ammoniated mercury ointment applied to the scalp. The next day extreme edema of the face and scalp appeared; this was followed later by edema of the hands and legs. Sometime later an urticarial eruption appeared over the entire body. This same patient a year later had some ammoniated mercury ointment applied to an abrasion over a fresh scar. The ointment was immediately removed, but the following day edema of the face and hands appeared and was accompanied by pruritus and a generalized erythema. A number of months later this same patient exhibited the same symptoms after handling a small glass funnel through which some metallic mercury had been poured a few minutes before she handled it.

Wilbar [8] reported on an 18 month old patient who had received daily applications of a 15 per cent ammoniated mercury ointment. After seven days a rash appeared and spread rapidly. The use of the ointment was continued for ten days more, by which time a generalized scaling and crusting lesion appeared. This patient excreted 0.2 mg. of mercury in 50 cc. of urine, or 4 mg. per liter of urine, but retained good urinary function. This patient acquired a generalized exfoliative dermatitis, stomatitis and edema and cyanosis of the hands and feet.

REPORT OF CASES

Case 1.—A 22 month old white girl was admitted to the pediatric service of the Brooklyn Jewish Hospital on Sept. 20, 1942. She had been in good health until two weeks before her admission, at which time impetigo developed about the face and neck. For this she was taken to a dermatologic clinic and given a preparation of 5 per cent ammoniated mercury ointment. The impetigo responded well to treatment. On September 18, after eleven days of treatment, a generalized erythematous morbiliform eruption and a temperature of 104 F. developed. The eruption was thought to be measles by the family physician. The following day the rash appeared punctate in character and was thought by a second physician to be scarlet fever. She was given sulfadiazine at this time. On the third day after the erythema appeared, blisters were noted scattered everywhere about the body. Some of them were almost as large as bullae.

On the patient's admission to the hospital her temperature was 102° F. She was acutely ill. The skin presented a deep erythematous eruption and was thick and indurated. Over the extremities the erythema was morbilliform. The scars of the impetigo were still present on the face and neck. The face was covered with numerous excoriated, crusted bleeding areas. The remainder of the body was covered with numerous blisters and bullae, varying in size from that of a green pea to that of a silver dollar. The examination otherwise revealed normal conditions; the spleen was not palpable. The superficial lymph nodes were not enlarged. The blood on admission was sterile; the urine contained a trace of albumin. The hemoglobin content was 74 per cent; the red blood cell count, 4,200,000, and the white blood cell count, 15,800, with 82 per cent polymorphonuclear cells and 18 per cent lymphocytes.

During the first two days in the hospital the patient was toxic and listless. On the third day her temperature started to climb and reached 104 F. Administration of sulfathiazole was started on the fourth day because of the fear of sepsis but was discontinued on the eleventh day, after blood cultures remained sterile. At this time her temperature had returned to normal. No therapy was used except restraints to keep the child from scratching. On the second day the skin began to show signs of improvement, and by the third day the blisters and bullae were beginning to dry up. By the ninth day improvement was marked; all of the blisters had opened and were drying, and the skin over the entire body was desquamating.

Subsequently the skin over the entire body desquamated. At the time of her discharge, on the twenty-fifth day, some areas of induration and erythema were still present about the toes and fingers but the remainder of the skin was normal.

Albumin was not detected in the urine after the first specimen.

8. Wilbar, C. L., Jr.: Mercury Poisoning from Topical Application of Fifteen Per Cent Ammoniated Mercury: Report of a Case, J. Pediat. **20**:89-92 (Jan.) 1942.

Two days before the child's discharge a patch test with 5 per cent ammoniated mercury was performed. The tested area became reddened after seven days and remained red for twenty-four hours.

CASE 2.—This patient was a 14 month old white boy. He had been brought to his physician because an ammoniated diaper rash and an external meatitis had developed. The mother was instructed to rinse the diapers in a solution of mercury bichloride, using one 7½ grain (0.49 Gm.) tablet to 2 quarts (1.9 liters), of water, to make a 1:4,000 solution. This solution was to be the final rinse before the diapers were hung up to dry. She was instructed to follow that procedure for two or three days. However, the mother was so well pleased with the rapid disappearance of the ammoniacal dermatitis that she continued to use the mercury bichloride rinse.

On the sixth day of use a marked erythema limited to the diaper area developed. The next day the skin in that area became indurated, and the patient's temperature rose to 102 F. At the same time a scattered macular eruption appeared on the face and chest. On this day the child was again seen by his physician and the use of the mercury bichloride rinse was discontinued. The patient had become extremely restless, and the rash had spread to cover the entire body. In places the lesions were coalescent so as to resemble scarlet fever, and in other areas the eruption was morbilliform. The temperature continued to climb until it reached 106.2 F. Within three days after the rash appeared the entire body was covered, and on the fourth day blisters began to appear in the diaper area, behind the lobes of the ears and on the neck. On the fifth day the blisters on the perineum began to break, so that the entire area was denuded of superficial skin. Five per cent boric acid ointment was used locally to prevent clothes from adhering to the skin.

The urine remained normal throughout, and except for suppression during the third day, when only 3 ounces (90 cc.) of urine was passed, no abnormalities were detected. The blood picture remained normal throughout, and eosinophilia was not encountered.

On the sixth day desquamation started, and in about fourteen days the skin was normal again.

COMMENT

Reactions to preparations of mercury occur infrequently in children, but they do occur. The literature contains reports of reactions to ammoniated mercury, mild mercurial ointment U. S. P., mild mercurous chloride and metallic mercury, and to the mercury in amalgam fillings used in teeth. The cutaneous reactions may vary from a slight erythema to a severe generalized eruption. Thus, the eruption may be morbilliform; it may be punctate and resemble scarlet fever, or it may be urticarial. Blisters may appear and go on to form bullae. The color of the skin may vary from light pink to dark red. Frequently the skin desquamates in large sheets; it may crack and ooze, and scales may develop. Pruritus can be extremely annoying and difficult to control, and secondary infections may be introduced by scratching.

Constitutional symptoms may be severe, and extreme prostration may be accompanied by high fever and toxicity. Delirium may occur but is uncommon. The blood smears as a rule do not show an increased number of eosinophils, and the urine contains only a trace of albumin.

It is not unusual for a patient to be susceptible to one compound of mercury and not to another. On the other hand, the same patient may get different reactions depending on the type of drug used. Thus, one patient acquired a scarlatiniform eruption from mild mercurous chloride, but urticaria developed from mild mercurial ointment.

The interval between the application of the drug and the appearance of the eruption has varied in reported cases from one to twelve days.

TREATMENT

Treatment consists primarily of withdrawing the offending mercury preparation. If the reaction is mild, that is all the treatment that is required. With severe reactions, after withdrawal of the drug precaution must be taken to prevent

scratching of the skin. Restraints are used if necessary and sedation as required. Fluids must be forced, preferably by mouth. Intravenous injection or hypodermoclysis of fluids should be avoided if the needle has to penetrate involved skin, because of the danger of introducing a secondary infection. Local applications to the skin should be avoided as far as possible, as bland ointments and lotions may macerate the already injured skin. When thick crusts of dried serum appear, moist boric acid dressings may be used to soften them. Secondary infections may be treated with wet compresses or sulfathiazole ointment. Preferably the patient should be kept undressed and on a sterile sheet. The bedclothes should be supported by a cradle to prevent their contact with the skin.

It is gratifying to note that, although some very severe reactions have been described, no case of death caused by the local application of a mercury preparation to the unbroken skin has been reported.

SUMMARY

Idiosyncrasies to various preparations of mercury have been reported. These include reactions to ammoniated mercury ointment (1 to 15 per cent), mild mercurial ointment U. S. P., mild mercurous chloride, metallic mercury and amalgam.

Reactions varying from a mild erythema to a severe generalized eruption with correspondingly severe constitutional symptoms may appear.

The reactions are due to a true idiosyncrasy, not to poisoning.

The amount of mercury absorbed through the unbroken skin is usually very small.

The period between the application of the drug and the appearance of the rash may vary from one to eleven days.

Twelve cases of idiosyncrasy to ammoniated mercury ointment have been reported from 1883 to 1942.

A case of idiosyncrasy to ammoniated mercury ointment and a case of idiosyncrasy to mercury bichloride solution (1:4,000) are recorded.

Case 2 is reported by permission of Dr. Nathan R. Kahn, of Brooklyn.

Photographs by Mr. W. L. Abbey, of the Art Department.

Progress in Pediatrics

EXPERIMENTAL BASIS FOR TREATMENT OF HAEMOPHILUS INFLUENZAE INFECTIONS

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The influenza bacillus was first isolated by Pfeiffer during an epidemic of 1889. The frequency of its occurrence led to the erroneous deduction that it was the cause of the disease. The modern presumption is that the epidemic was the work of a virus. Nonetheless, the concept that this bacterial organism was the primary agent led to the misleading name, Haemophilus influenzae, which it unfortunately retains today. During the last decade the primary pathogen in numerous epidemics of influenza of more or less limited scope has been shown to be a virus. However, extensive bacteriologic studies carried out during the 1918 influenza pandemic demonstrated the great importance of H. influenzae as a secondary invader. This evidence was completely reviewed by Jordan [1] in his book "Epidemic Influenza." A number of investigators of this pandemic expressed the opinion that its unparalleled severity was due to the concurrent reappearance of the epidemic form of the influenza virus and the influenza bacillus. The periodic incidence of pandemics, together with circumstances created by the present war, has led some epidemiologists to predict another epidemic for the near future. This has stimulated interest in the future role of the influenza bacillus.

Pittman's [2] contributions in 1931 laid the foundation for the progress which has been made in the study of H. influenzae infections during the past ten years. She showed that the strains of H. influenzae prevalent in the healthy human respiratory tract differed from those isolated from persons with a H. influenzae infection. The pathogenic strains could be differentiated from nonpathogenic forms by their production of iridescent growth on Levinthal agar plates. Strains showing this characteristic possessed capsules; the capsule contained the carbohydrate specific for each type. Six different types were identified by precipitin tests, which demonstrated the presence of the specific soluble carbohydrate, and by agglutination tests carried out according to a special technic. The six types were designated a, b, c, d, e and f.

It is unfortunate that the strains of H. influenzae which were isolated during the 1918 epidemic could not be investigated according to these more modern criteria. In the light of present knowledge it appears highly probable that the strains which were isolated in pure culture from the lungs and blood of patients

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1. Jordan, E. O.: Epidemic Influenza: A Survey, Chicago, American Medical Association Press, 1927.

2. Pittman, M.: Variation and Type Specificity in Bacterial Species Hemophilus Influenzae, J. Exper. Med. **53**:471 (April) 1931.

in those days must have been encapsulated or typable forms. Whether the frequency of occurrence of iridescent strains in the respiratory tract differed from the previous or subsequent experience cannot be answered. However, in many areas of the country the prevalence of all strains of H. influenzae at that time was far greater than has ever been demonstrated since. The observations of Dochez [3] and his associates on the chimpanzee suggest that such circumstances may in fact herald the outbreak of an epidemic. Under ordinary circumstances the bacterial flora of the upper respiratory passages of this animal is characteristically similar to that found in man. Inoculation of the virus of the common cold into a chimpanzee produces a number of changes which have been studied in detail, among them the conversion of nonencapsulated, and therefore presumably nonpathogenic, strains of H. influenzae into encapsulated or potentially pathogenic forms.

The importance of type b H. influenzae as a cause of meningitis has been well known since the pioneer work of Pittman. The role which this organism plays in childhood infections outside the central nervous system has come to be appreciated only within the past few years. Virtually all of the serious H. influenzae infections in infants and children appear to be caused by type b organisms. Recently the potential importance of the prevalence of H. influenzae in conjunction with future virus epidemics has stimulated interest in its occurrence in patients at the Babies Hospital.

Materials for culture are taken from the throat and the nasopharynx by the passage of a wire applicator through the nose to the posterior pharyngeal wall, as reported previously.[4] After withdrawal of the applicator, it is placed in a tube containing 0.2 cc. of plain broth so as to make a concentrated suspension of mucus, which is then used for inoculating the surface of a blood agar plate and a tube of blood broth. The swab itself, after being freed of mucus, is transferred to Levinthal broth containing 0.1 per cent sodium oleate. After twenty-four hours' incubation, suspicious colonies on the plate are streaked on Levinthal agar and inoculated into Levinthal broth. Colonies producing iridescent growth on Levinthal agar are then tested for type specificity by the capsular swelling test with six diagnostic typing serums. Transplants from colonies which fail to produce iridescence are studied for their requirements of X and V growth factors. The need for both of these factors furnishes proof that a given organism is H. influenzae. Recent investigations have identified X factor as hematin and V factor as coenzyme. The blood broth and sodium oleate broth at the end of twenty-four hours' incubation are streaked on blood agar plates and handled in the manner described.

The procedures have been described in some detail for the reason that the frequency of isolation of H. influenzae in any laboratory depends on the cultural methods used and on the interest displayed by the working team. It is clear that the addition of sodium oleate enhances the opportunity for isolation. On the other hand, in acute infections due to H. influenzae this adjunct is unnecessary. In fact, when a child is suffering from a severe H. influenzae infection, the suspension of mucus from his nasopharynx may serve as an excellent source for almost immediate identification of type b organisms by the capsular swelling test.

Results of this investigation, covering a period of one and a half years, are presented in table 1. It is seen that 217 of the 847 children studied harbored H. influenzae in the respiratory tract. One hundred and seventy-six of the strains isolated were noniridescent and nonencapsulated. Forty-one, or 5 per cent, of all

3. Dochez, A. R.; Mills, K. C., and Kneeland, Y., Jr.: Variation of H. Influenzae During Acute Respiratory Infection in Chimpanzee, Proc. Soc. Exper. Biol. & Med. **30**:314 (Dec.) 1932.

4. Alexander, H. E.; Craig, H. R.; Shirley, R. G., and Ellis, C.: Validity of Etiological Diagnosis of Pneumonia in Children by Rapid Typing from Nasopharyngeal Mucus, J. Pediat. **18**:31 (Jan.) 1941.

children for whom cultures were made had typable H. influenzae organisms in the respiratory tract. Eighteen per cent of strains of H. influenzae isolated were typable. There is no evidence of seasonal fluctuation in prevalence.

Infections due to type b H. influenzae organisms constitute a serious problem in childhood. At the present time there is a striking difference between the pathologic potentialities of this organism in adults and in children. The adult appears to possess effective resistance to it. Fothergill [5] secured evidence on this point by testing the bactericidal power of the blood of persons of various ages. In infancy and early childhood, when the incidence of H. influenzae meningitis is highest, the blood of subjects collected at random shows but feeble bactericidal capacity toward organisms of this group, whereas older persons have a relatively high titer of specific antibodies and possess at the same time an appreciable

TABLE 1.—*Incidence of H. Influenzae in 847 Children*

Year, 1941	Total Number Cultured	H. Influenzae		Nontypable H. Influenzae	Typable H. Influenzae
		Number	Percentage		
June and August	121	39	32	32	7
October to December	200	55	28	42	13
1942					
January to April	369	96	26	83	13
May to September	157	27	17	19	8
	847	217	25	176	41

TABLE 2.—*Source of Typable Strains*

Types	No Evidence of Infection	Infection of Respiratory Tract	Severe Infections *	Total
a	2	1	..	3
b	5 (16%)	9 (29%)	17 (55%)	31
c	1	..	..	1
d	1	..	..	1
e	..	2	..	2
f	2	1	..	3
	11	13	17	41

* Infections included in this group: (1) ethmoid sinusitis with periorbital cellulitis and bacteremia; (2) obstructive infections of respiratory tract; (3) pneumonia with bacteremia; (4) meningitis.

immunity to infections caused by these organisms. However, there is reason to believe that should the normal defense mechanism be altered, as has been shown to occur in severe epidemics of influenza, a greater prevalence of severe H. influenzae infections in adults is to be expected. The circumstances under which type b organisms have been isolated during the last one and one-half years at the Babies Hospital are presented in table 2, together with the sources of other types which were identified.

Seventy-eight per cent of all typable forms recovered were of type b; of these, 55 per cent originated from gravely ill children. In the remaining 22 per cent the 5 other types were represented, but they occurred in children with infections of the upper respiratory tract or in children without signs of infection. On the other hand, patients with H. influenzae meningitis due to types a and f are encountered

5. Fothergill, L. D., and Wright, J.: Influenzal Meningitis: Relation of Age Incidence to Bactericidal Power of Blood Against Causal Organism, J. Immunol. **24**:273 (April) 1933.

occasionally. Only 41 per cent of all typable strains were isolated from children with severe infections; all of these were type b. Twenty-nine per cent of the children from whom type b organisms were isolated had febrile infections of the upper respiratory tract. Pneumonia was not demonstrated, though only 2 had roentgen examinations. Cough was a prominent symptom. Profuse nasal discharge was also conspicuous, suggesting sinusitis. These children recovered promptly after the administration of a sulfonamide compound. In 5 of the children, or 16 per cent of the series, with type b organisms there were no signs of significant infection at the time, although in 3 instances there had been frequent infections of the respiratory tract in the recent past. It is too early to draw conclusions, for the group yielding type b organisms is still small. However, the results suggest that a large number of children overcome infection of the upper respiratory tract due to type b H. influenzae satisfactorily without medical aid.

Clinical evidence suggests that sinusitis is the most frequent complication of type b nasopharyngitis. Any part of the lower respiratory tract from the epiglottis to the alveoli may be involved as the principal primary lesion. Rarely in older children otitis may occur, with or without involvement of the bronchial tree. This is a frequent complication of the advanced stage of meningitis. In infants and children these lesions of the respiratory tract are commonly accompanied by bacteremia; in consequence, suppurative arthritis, meningitis and rarely peritonitis and pericarditis may develop.

The severe infections which are encountered with a fair degree of frequency in children are meningitis, obstructive infections of the respiratory tract and pneumonia accompanied by empyema in infants under 1 year of age. The following paper will deal with the treatment of these forms of the disease, together with a brief discussion of pneumococcic and meningococcic meningitis. I have included the latter for the reason that the same fundamental principles apply to the treatment of all three varieties of meningitis.

This paper will attempt to furnish a background for a rational therapeutic approach to these infections.

Four years ago at Babies Hospital there was adopted for treatment of type b H. influenzae meningitis a combination of a sulfonamide compound with type-specific rabbit serum. This decision was taken for the following reasons: The pioneer work of Pittman [2] had demonstrated a striking biologic similarity between the pneumococcus and H. influenzae, suggesting that in infection with the influenza bacillus, as well as with the pneumococcus, type-specific antibody is an essential part of the recovery mechanism. Horsfall and Goodner [6] had shown the superiority of antipneumococcus rabbit serum over antipneumococcus horse serum. The importance of the quantitative approach to serum therapy in this disease had already been established. The sulfonamide compound was used in addition to rabbit antibody on the grounds that the high fatality rate justified a combination of all potentially effective agents. The spontaneous mortality in large series had varied from 92 to 100 per cent when all age groups were considered.

Evidence will be presented for the conclusion that the combination of a sulfonamide compound and type-specific rabbit serum is the treatment of choice for all severe H. influenzae infections in children. Three sources have provided arguments for the effectiveness of these agents: first, investigation of the biologic features of H. influenzae; second, comparison of the protective value in mice

6. (*a*) Horsfall, F. L., Jr.; Goodner, K., and MacLeod, C. M.: Type Specific Antipneumococcus Rabbit Serum, Science **84**:579 (Dec. 25) 1936. (*b*) Horsfall, F. L., Jr.; Goodner, K.; MacLeod, C. M., and Harris, A. H., Jr.: Antipneumococcus Rabbit Serum as Therapeutic Agent in Lobar Pneumonia, J. A. M. A. **108**:1483 (May 1) 1937.

of the therapeutic agents singly and combined, and, third, the results obtained when these agents are combined in the treatment of meningitis in children. The first two will be discussed in this paper. The third will be presented in the following paper.

BIOLOGIC FEATURES OF H. INFLUENZAE

I. *Production of Specific Polysaccharide.*—Pittman reported in 1931 that production of a soluble specific polysaccharide was responsible for type specificity and pathogenicity of H. influenzae. By means of special stains she demonstrated that one of the distinctive features of pathogenic strains is the presence of a capsule. Early in my studies [7] it was shown that strains of this organism responsible for acute infections could be typed by the capsular swelling method, which facilitated their immediate identification in all biologic fluids containing a number of organisms sufficient for demonstration in stained smear. The method is identical with the Neufeld procedure for typing pneumococci. My experience with human infections suggests that a crude estimate of the concentration of specific soluble carbohydrate in the body fluids is an index of severity and therefore of antibody requirements. The capsular swelling capacity of a patient's serum has served as a useful guide to sufficiency of a given dose of antibody.

II. *Protective Element of Serum—Anticarbohydrate Antibody.*—Attempts have been made to determine whether or not the protective or curative antibody is actually anticarbohydrate. By analogy with pneumococcus antibody this was at first assumed to be true. The quantitative determination of precipitin nitrogen devised by Heidelberger [8] for determining the amount of antibody in therapeutic type b rabbit serum measured the anticarbohydrate antibody in terms of milligrams of antibody nitrogen per cubic centimeter. This method, together with that designed to identify agglutinin nitrogen, will be described later. The volume of a given solution of antibody administered to a patient was based on these figures.

This assumption that anticarbohydrate antibody represents the protective element in therapeutic serum has now been subjected to experimental study.[9] Samples of type b H. influenzae rabbit antiserum which had been analyzed for their content of agglutinin and precipitin nitrogen were absorbed with specific polysaccharide isolated from broth cultures of type b H. influenzae. Mouse protection tests were performed to test the power of absorbed and unabsorbed serum to protect mice against lethal H. influenzae infections.

It appears from the results that essentially all the protective power of a serum is removed when virtually complete absorption of anticarbohydrate antibody has been effected, as judged by content of agglutinin and precipitin nitrogen. Therefore, these quantitative analytic methods which measure the anticarbohydrate antibody actually measure the protective substance against type b H. influenzae infections in mice.

III. *Superiority of Rabbit Antibody Over Horse Antibody.*—Therapeutic results suggest that rabbit type-specific antibody is superior to horse antibody in the treatment of H. influenzae infections.

No experimental evidence for explanation of the superior therapeutic powers of H. influenzae rabbit serum is available. However, pneumococcus antibodies

7. Alexander, H. E.: Type b Anti-Influenzal Rabbit Serum for Therapeutic Purposes, Proc. Soc. Exper. Biol. & Med. **40**:313 (Feb.) 1939.

8. Alexander, H. E., and Heidelberger, M.: Chemical Studies on Bacterial Agglutination: Agglutinin and Precipitin Content of Antisera to Hemophilus Influenzae Type b, J. Exper. Med. **71**:1 (Jan.) 1940.

9. Alexander, H. E.; Heidelberger, M.; Leidy, G., and MacPherson, C.: Protective Element in Type b Hemophilus Influenzae Therapeutic Rabbit Serum, to be published.

from the rabbit and horse have been studied intensively. The size of the antibody molecule produced in the rabbit has been shown to be about one-fifth that produced in the horse. Horse antibody, when an optimal dose is exceeded, exhibits inhibition of protection in mice. This so-called prozone effect is not shown by rabbit antibody. Rabbit antibody combines with antigen in a much more efficient manner than does horse antibody. The practical significance of these attributes is obvious.

Horse H. influenzae antibody has been shown to be of the same order of magnitude as horse pneumococcus antibody.[10] The striking similarity of the biologic characteristics of these two organisms suggests that the sizes of the two rabbit antibody molecules are not very different. Moreover, the results of treatment of meningitis by the intravenous route indicate that the size of the antibody molecule permits its passage from the blood to the subarachnoid space.[11]

Examination of the spinal fluid of 12 patients who received a rabbit serum preparation by the intravenous route alone revealed the presence of antibody in each instance, though never in an amount sufficient to be demonstrable by the capsular swelling method. A more sensitive index was required. Agglutination tests were performed with suspensions of encapsulated organisms in a 0.5 per cent concentration of solution of formaldehyde U. S. P. in physiologic solution of sodium chloride. After mixture with the serum dilutions, the organisms were shaken for two minutes, incubated at 37 C. for two hours and iced for eight days before the final reading was made. It has been found that the smaller the amount of antibody present, the longer the period necessary for complete union of antigen and antibody.

IV. *Application of Quantitative Approach to Serum Therapy.*—The efficacy of anticarbohydrate antibody in the treatment of infections with type b H. influenzae must depend on the establishment in the patient of a satisfactory quantitative relationship between antigen, that is, the specific polysaccharide, and antibody, namely, the anticarbohydrate present in serum. This may be accomplished by three steps: first, making certain that the preparation of antibody used is potent; second, adapting the size of the dose to the severity of the infection, and, third, checking the sufficiency of the quantity administered.

1. Accurate Standardization of Serum Potency: The assay of the serum was first accomplished by Heidelberger,[8] who applied to H. influenzae antiserums quantitative chemical methods originally developed for determining the amount of antibody in pneumococcus antiserums. The potency is expressed in terms of milligrams of antibody nitrogen per cubic centimeter.

Analyses for anticarbohydrate precipitin were made by adding a slight excess of polysaccharide solution to an accurately measured volume of diluted serum and estimating the amount of nitrogen in the washed precipitate after forty-eight hours at 0 C.

The assay of agglutinin nitrogen depends on the addition of an accurately measured, washed suspension of bacteria to an accurately measured volume of antiserum, the relative amounts being so chosen that the bacteria are in excess. After agglutination is complete, the difference in nitrogen between the agglutinated bacilli, suitably washed, and the same number of unagglutinated bacilli gives in milligrams the agglutinin nitrogen content of the volume of serum chosen. An analysis of the supernatant liquid is also carried out, in order to make certain that

10. Treffers, H. P.: Personal communication to the author.

11. Alexander, H. E.; Ellis, C., and Leidy, G.: Treatment of Type-Specific Hemophilus Influenzae Infections in Infancy and Childhood, J. Pediat. **20**:673 (June) 1942.

all antibody has been removed. Seventy to 100 per cent of agglutinin nitrogen measured represents anticarbohydrate antibody. This method, which is simpler in some ways than the precipitin determination of nitrogen, is therefore satisfactory for practical purposes.

2. Appraisal of Severity of Infection: The evaluation of the severity of infection may be approached in two ways, depending on the clinical variety of the infection. A crude estimate of the concentration of specific soluble substance in the blood and spinal fluid may be arrived at. The total amount of antigen free in the body fluids plus the quantity of the same substance within the capsule of the organisms represents the amount which must be excreted or neutralized by antibody before recovery can take place. A direct measure of antigen is impossible. Only crude evaluation is feasible. Up to the present time my colleagues and I have made clinical use of serum concentration of polysaccharide as a guide in treating obstructive infections of the respiratory tract due to H. influenzae. Information is being accumulated on spinal fluid and urine. Over a 1 cm. column of

TABLE 3.—*Schedule of Dosage Based on Dextrose Content of Spinal Fluid*

Dextrose in Spinal Fluid, Mg. per 100 Cc.	Antibody Nitrogen Indicated, Mg.
<15	100
15 to 25	75
25 to 40	50
Over 40	25

TABLE 4.—*Qualitative Test for Estimating Sugar Content of Spinal Fluid in Milligrams Per Hundred Cubic Centimeters*

Tube Number	Cerebrospinal Fluid, Cc.	Reduction of Benedict's Solution					
1	0.05	+	0	0	0	0	0
2	0.1	+	+	0	0	0	0
3	0.15	+	+	+	0	0	0
4	0.2	+	+	+	+	0	0
5	0.25	+	+	+	+	+	0
Milligrams of sugar per hundred cubic centimeters		Over 50	40-50	30-40	20-30	10-20	<10

the diagnostic typing serum in a small precipitin tube an equal column of the body fluid under examination is carefully layered by means of a fine capillary pipet. A positive reaction consists in the formation of a white ring (precipitate) at the interface. Experience with this test on spinal fluid from patients with meningococcic meningitis suggests that the time of appearance of the white ring is an index to the amount of soluble specific substance present and is therefore a measure of the severity of the infection. The appearance of a ring within ten minutes is believed to represent a severe infection.

I have limited experience with use of this test on spinal fluid. However, as a matter of convenience a somewhat simpler method of appraising the severity of infection in meningitis is recommended for general use as a guide to the initial dose of antibody. This is based on the determination of the concentration of dextrose in cerebrospinal fluid. Table 3 represents an effort to adapt the amount of antibody required according to this criterion.

If the patient arrives during the night, when facilities for quantitative determinations of dextrose are not available, a simple qualitative method provides a satisfactory guide. This is shown in table 4.

3. Criteria for Sufficiency of Dose Administered: The third measure used for attaining the desired excess of antibody over antigen is the use of a laboratory method for checking sufficiency of the original dose of antibody decided on.

After administration of an original dose of standardized antibody the size of which is governed by signs of severity of infection, its sufficiency to the needs of any given patient with influenzal meningitis may be appraised by finding an adequate excess of antibody in the patient's serum. The capsular swelling capacity of the patient's serum has been shown to be satisfactory for this purpose. The excess of free antibody necessary for recovery is not known exactly. I have chosen an arbitrary standard. It is my aim to establish such an excess throughout the first week that the patient's serum when diluted 1:10 will cause capsular swelling.

A second method of determining excess of antibody is based on the use of type b carbohydrate in intracutaneous tests. Dingle and Seidman [12] have reported on the value of this procedure, and my results with several patients suggest a good degree of correlation with the capsular swelling capacity of the patient's serum. One-tenth cubic centimeter of 1:5,000 dilution of type b H. influenzae polysaccharide is introduced intracutaneously. A positive result, indicative of excess of anticarbohydrate antibody in the patient, is an immediate type of reaction (within five to ten minutes) which remains for approximately thirty minutes. This reaction is characterized by a wheal, with extrusion of pseudopods.

I have stated that three sources have provided evidence for the conclusion that the ideal treatment of severe type b H. influenzae infections in children is a combination of antibody and a sulfonamide compound. Before the second source of evidence for this conclusion, i. e. experimental work on mice, is discussed, an outline will be given of the available information derived from the use of these chemotherapeutic agents singly for patients.

The literature fails to provide data for assessing the value of the sulfonamide compounds in the treatment of H. influenzae meningitis without supplements of serum. Instances of recovery have been reported when each of the commonly used sulfonamide compounds has been used alone. Most of the publications include 1 or 2 cases, with summaries of previously reported cases. Such appraisals are misleading, for it is clear that individual successes are published more frequently than repeated failures. The only paper which contains data on a significant number of cases in one institution or vicinity with treatment exclusively by chemotherapy is that of Aleman, who reported 18 cases in which treatment was with sulfapyridine alone, with a mortality of 72 per cent. Of 50 cases with treatment only with sulfanilamide gathered from the literature and from the author's experience, 88 per cent terminated fatally. Unless a reported series is analyzed with regard to the ages of the patients and unless the severity of the infections is evaluated on laboratory evidence, it is not possible to estimate the true efficiency of the therapy used.

Table 5 presents the data for a group of patients who received rabbit antibody and a sulfonamide compound after prolonged periods of unsuccessful treatment by chemotherapy alone or combined with horse serum. The duration of previous treatment is tabulated. The recovery of 12 of these 18 patients after treatment with rabbit antibody permits two conclusions:

1. All the sulfonamide compounds used thus far exert a significant inhibitory effect on H. influenzae infections in children.

12. Dingle, J. H., and Seidman, L. R.: Specific Polysaccharide as Cutaneous Test for Evaluation of Serum Therapy in Influenza Bacillus Meningitis, Proc. Soc. Exper. Biol. & Med. **46**:34 (Jan.) 1941.

2. Type-specific antibody is an essential part of therapy for a number of patients with H. influenzae meningitis. The proportion is not yet known.

The evidence suggests that the capacity of the sulfonamide compounds to effect complete recovery from the generally severe H. influenzae infections is conditioned by two factors: Use of the drug must be started early in the course of the infection, and the infection must be of relatively mild degree. It is believed that only under such circumstances can the patient produce by himself sufficient antibody to overcome the infection. My colleagues and I have shown production of agglutinin by the host in 2 patients who recovered from meningitis with treatment by a sulfonamide compound alone and in 1 patient with type b H. influenzae pneumonia which responded promptly to sulfadiazine.

Lack of information on the severity of meningitis in patients reported to have recovered with treatment by a sulfonamide compound and the difficulties encountered in evaluating the efficiency of the various single therapeutic agents in patients have led us to test the protective value of sulfonamide compounds and serum separately and in combination against H. influenzae infections in mice.

A preliminary report [13] of these results has already been presented. Pittman [14] has subsequently published similar results.

TABLE 5.—*Patients Treated in Other Hospitals with Other Forms of Therapy for Long Periods Prior to the Use of Type b Rabbit Antibody*

Duration of Meningitis Before Administration of Rabbit Serum	Results of Treatment		
	Recovery	Death	Total
2 weeks	2	3	5
3 weeks	3	2	5
4 weeks	4	1	5
5 weeks	1	0	1
6 weeks	1	0	1
7 weeks	1	0	1
Total	12	6	18

Sulfanilamide, sulfadiazine and antibody singly and sulfadiazine combined with antibody have been compared as protective agents against this infection in mice. All agents to be tested were introduced prior to the injection of organisms. Antibody was administered in a single dose intraperitoneally. The drugs were introduced through the esophagus directly into the stomach of the mice by means of a blunt 18 gage needle attached to a 1 cc. syringe. This route was decided on for the reason that it was found to maintain more satisfactory blood levels than intraperitoneal or subcutaneous routes. Introduction of the drug through the food was unsuccessful. The mice refused the food because they became sick. All mice receiving a sulfonamide compound were given two doses daily. Sulfanilamide was used in a dosage of 1 Gm. per kilogram of body weight daily for three days. When this dose was exceeded, the mice died from the toxic effect of the drug. Sulfadiazine was well tolerated in a dose of 2 Gm. per kilogram per day.

Table 6 presents the results of a single test comparing all of these agents at one time against the same suspension of organisms.

13. Alexander, H. E.; Ellis, C., and Leidy, G.: Treatment of Type-Specific Haemophilus Influenzae Infections in Infancy and Childhood, Am. J. Dis. Child. **64**:386 (Aug.) 1942.

14. Pittman, M.: Antibacterial Action of Several Sulfonamide Compounds on Hemophilus Influenzae Type b, Pub. Health Rep. **57**:1899 (Dec. 11) 1942.

The first few experiments, even though they were based on only 5 mice per dilution, showed a consistent superiority of sulfadiazine over sulfanilamide. For this reason our effort was concentrated on the problem of comparison of the protective action of sulfadiazine and of antibody singly and combined.

Table 7 presents the results of a similar test which used 10 mice per dilution. These results are representative of those of two other experiments which are duplicates of this. Several features are of interest. They fail to show a significant difference between the influence of sulfadiazine and that of antibody. The protective power of these agents when combined is superior to that obtained with

TABLE 6.—*Comparative Test with Several Sulfonamide Compounds (5 Mice per Dilution)*

Protective substance	Dosage of Organisms (Expressed in M. L. D.—L_{50})*															
	10^6		10^5		10^4		10^3		10^2		100		10			
	Dilutions of Standard															
	10^{-2}		10^{-3}		10^{-4}		10^{-5}		10^{-6}		10^{-7}		10^{-8}		10^{-9}	
	D	S‖	D	S	D	S	D	S	D	S	D	S	D	S	D	S
Sulfanilamide †	..	..	..	..	..	..	5	0	4	1	0	5	..	..	..	..
Sulfadiazine ‡	..	..	..	..	4	1	2	3	0	5	..	..	..	..	..	..
Serum §	..	..	..	..	4	1	1	4	1	4	..	..	..	..	..	..
Sulfadiazine and serum	5	0	1	4	1	4	0	5	..	..	..	..	..	..	..	..
Control	..	..	..	..	..	..	..	..	..	..	4	0	5	0	3	2

* Colony count of standard suspension, 1,380,000,000 per cubic centimeter.
† Dose, 0.5 Gm. per kilogram twice daily for three days.
‡ Dose, 2 Gm. per kilogram first day; 0.6 Gm. per kilogram daily on second and third days.
§ Dose, 0.6 cc. of 1:100 dilution = 0.009 mg. antibody N.
‖ D, deaths; S, survivals.

TABLE 7.—*Comparative Test with Several Sulfonamide Compounds (10 Mice per Dilution)*

Protective substance	Dosage of Organisms (Expressed in M. L. D.—L_{50})*															
	10^6		10^5		10^4		10^3		10^2		100		10			
	Dilutions of Standard															
	10^{-2}		10^{-3}		10^{-4}		10^{-5}		10^{-6}		10^{-7}		10^{-8}		10^{-9}	
	D	S‖	D	S	D	S	D	S	D	S	D	S	D	S	D	S
Sulfadiazine †	..	..	10	0	6	4	2	8	..	..	..	..	..	..	..	..
Serum ‡	..	..	9	1	6	4	3	7	..	..	..	..	..	..	..	..
Sulfadiazine and serum	8	2	2	8	1	9	..	..	..	..	..	..	..	..	..	..
Control	..	..	..	..	..	..	..	..	..	..	8	2	7	3	5	5

* Colony count of standard suspension, 1,600,000,000 per cubic centimeter.
† Dose, 2 Gm. per kilogram first day; 0.6 Gm. per kilogram daily on second and third days.
‡ Dose, 0.6 cc. of 1:100 dilution = 0.011 mg. antibody N.
‖ D, deaths; S, survivals.

either alone. These results are supported by a number of experiments which will be summarized later. They demonstrate, as do other tests, the importance of the size of the infecting dose. Other experiments in which larger doses of antibody or sulfadiazine given alone have been administered have not increased the protection significantly. Likewise, when the size of the dose of the two combined agents has been increased, protection has not been greater. Our experience in the treatment of human infections convinces us that this is true for an occasional patient. After it is admitted that beyond this fact our knowledge ceases, it seems permissible to bring up for consideration the influence of the toxic substances within or elaborated by the influenza bacillus. Dubos[15] has prepared a toxic

15. Dubos, R. J.: A Soluble Toxin Produced by Hemophilus Influenzae, J. Bact. **43**:77 (Jan.) 1942.

substance from H. influenzae which is antigenic and stimulates the production of an antibody which has protective power. It is hoped that this approach will provide help in the crossing of this hurdle. However, investigation along these lines in the treatment of infections due to other organisms which show similar biologic characteristics has been disappointing.

Table 8 presents a summary of the results of all protective experiments which have tested the power of these agents.

The numbers representing the comparative values are the average protection expressed in L_{50} minimum lethal doses (minimum lethal doses based on 50 per cent fatality). These were obtained from a series of tests. The numbers of mice used in obtaining these figures are listed for each value. While it is believed these numbers represent the best available information under the circumstances, they must be viewed only as approximations, and it must be kept in mind that the experiments were performed on mice. However, they suggest certain conclusions:

1. When sulfanilamide and sulfadiazine are administered in the doses indicated, sulfadiazine affords superior protection in mice. Comparable blood levels of the two drugs were present at the time of injection of organisms. However, the concentration of sulfanilamide was poorly sustained in the mice receiving this drug. Preliminary tests on mice receiving doses of sulfadiazine resulting in blood

TABLE 8.—*Summary of Protective Power of Therapeutic Agents in Mice*

Therapeutic Agent	Protection	
	L_{50}	No. of Mice
Sulfanilamide	500	120
Sulfadiazine	9,250	280
Serum	28,875	625
Sulfadiazine + serum	850,000	270

levels comparable to those of sulfanilamide-treated mice yielded a degree of protection equivalent to that in mice receiving the quantities of sulfadiazine specified in the experiments just described. Comparison of the maximal protection by these drugs is complicated by the fact that sulfanilamide in quantities greater than 1.5 Gm. per kilogram in twenty-four hours proves toxic to mice whereas a dose of 3 Gm. per kilogram of sulfadiazine is well tolerated.

2. It has not been possible to demonstrate a striking difference between the average protection afforded by sulfadiazine administered daily for three days and serum given intraperitoneally in one dose when each is used alone. The figures indicate that the protective power of antibody is three times that of sulfadiazine. However, since the variation between individual tests may be as great as 10, this difference cannot be taken as significant.

3. When these two agents are combined, it is obvious that the results are superior to those obtained with either alone.

The expense involved and the experience required for satisfactory mouse protection tests are so formidable that I have compared the results obtained thereby with the less costly test tube assay of effectiveness. Sulfanilamide, sulfapyridine and sulfadiazine have been compared. This work is in progress, and the number of strains examined is not sufficient for drawing conclusions or for numerical charting. There is as yet no indication that a correlation exists between the duration of exposure of a strain to a sulfonamide compound in the host and its resistance to the same agent in vitro. However, the results thus far suggest that this method

will prove useful in studying the susceptibility of various strains to sulfonamide compounds.

The results of in vitro comparison parallel the results obtained in protection tests on mice in at least one respect. Sulfadiazine has proved superior to sulfanilamide against all six strains tested in duplicate. Sulfapyridine occupies an intermediate position.

SUMMARY

Results of an investigation of the prevalence of H. influenzae in 847 children over the past one and a half years have been presented. Some variety of H. influenzae inhabited the respiratory tract of 25 per cent of all children for whom cultures were made. Encapsulated forms, on the other hand, including all types, were recovered from only 41, or 5 per cent, of the 847 children. Seventy-three per cent of these were sick, 43 per cent with acute febrile infections of the upper respiratory tract and 57 per cent with severe infections. All of the latter were caused by type b organisms. This study suggests that type b H. influenzae infections follow the pattern of virus and bacterial diseases in general. Mild infections are as frequent as the severe variety.

Three sources of evidence have been presented for the conclusion that a combination of type-specific antibody and sulfadiazine is the ideal treatment for severe type b H. influenzae infections in children:

I. Study of the biologic features of H. influenzae suggest that type-specific antibody plays an important role in recovery from this infection. It has been shown that the satisfactory quantitative relationship between antigen and antibody aimed for in serum treatment may be accomplished in three steps:

1. Use of a therapeutic product which has been assayed by quantitative chemical means. I have presented evidence that this method actually measures the protective element when it quantitates the anticarbohydrate antibody.

2. Use of laboratory criteria for the severity of infection.

3. Check of the sufficiency of a given dose by examining the patient's serum for satisfactory excess of free antibody (the capacity to produce capsular swelling when diluted 1:10 has been adopted as the desirable excess). The reaction of the patient to intracutaneous injection of the specific carbohydrate also provides this information.

II. Influence of the available agents on the type b H. influenzae infection in mice and growth in the test tube have been offered as the second source of evidence leading to the stated conclusion.

The protective capacity of sulfanilamide, sulfadiazine and antibody singly and of a combination of sulfadiazine and antibody have been compared against lethal type b H. influenzae infections in mice. The results justify the following conclusions: Protection afforded by sulfadiazine was superior to that of sulfanilamide; sulfadiazine and antibody separately did not differ significantly in this capacity; the combination of these two agents, on the other hand, was consistently superior to either agent when used alone.

Limited experience with the in vitro influence of sulfanilamide and sulfadiazine suggests that in at least one respect there is a correlation between the results obtained by this method and the capacity to protect mice. Sulfadiazine has been found superior to sulfanilamide in its inhibitory power against all strains tested.

III. The results of treatment of these infections in children have furnished the third source and are presented in the next paper.

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TREATMENT OF HAEMOPHILUS INFLUENZAE INFECTIONS AND OF MENINGOCOCCIC AND PNEUMOCOCCIC MENINGITIS

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Incredible as it may seem, five years ago the accepted routine in most hospitals for any patient found to have cloudy spinal fluid by gross inspection was the immediate intrathecal administration of antimeningococcus horse serum. This reflects the hopeless attitude which was shared by all regarding the treatment of pyogenic meningitis other than that caused by meningococci. Moreover, the mortality of meningococcic meningitis varied from 20 to 50 per cent in representative series. Serum was used according to methods now viewed as inadequate for the evaluation of antibody as a therapeutic agent: First, it was assayed by agglutination tests, and these were performed by methods which it is now known failed to detect type-specific antibody; second, no effort was made to adapt the size of the dose to the severity of the infection or to check the sufficiency of a given dose of serum after it had been administered; third, the superiority of rabbit serum was not appreciated. For these reasons little information was acquired of the potentialities of specific serum when used in adequate quantities.

In this short space of five years the miracles accomplished by sulfonamide compounds have changed the whole method of approach and the prognosis for most bacterial meningitides. It is clear from investigations on the underlying mechanism that sulfonamide compounds exert their curative effect not by direct lethal action on the organisms but rather by interfering with their metabolism. After such an inhibitory action the natural defense mechanisms of the body become more effective.

Today physicians are in the fortunate position of having access to one therapeutic agent which serves as a satisfactory initial treatment for all common varieties of pyogenic meningitis. The broad range of action of sulfadiazine, together with the infrequency with which it causes serious toxic manifestations, makes it the initial medicament of choice. If an infectious agent is susceptible to any of the previously popular sulfonamide compounds, there is reason to believe that it will respond at least equally well to sulfadiazine. This drug is consequently a great comfort to the physician who first sees the patient with signs of meningeal irritation. He is aware that the more severe the infection the more important is early treatment. Yet there are no clinical signs which enable him to differentiate one variety of pyogenic meningitis from another with the exception of the petechial cutaneous manifestations characteristic of meningococcic bacteremia. In Haemophilus influenzae meningitis, for instance, fulminating infections identical with those seen in meningococcic infection, except for absence of the petechiae, are frequently observed. On the other hand, the clinical features of tuberculous meningitis may be duplicated by meningitis caused by H. influenzae; between these two extremes all varieties

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occur. There is justification, then, supported by experimental and clinical proof, for the immediate administration of sulfadiazine when the patient presents the picture of meningitis.

The present paper reviews the treatment of H. influenzae infections and of meningococcic and pneumococcic meningitis. These were selected for two reasons: First, they are encountered more frequently than other types of pyogenic meningitis; second, the infectious agents possess similar biologic features, which depend to a great extent on a similar pattern of chemical structure. Each of these organisms is enveloped by a layer of polysaccharide. It has been generally considered that the periphery of this layer is outlined by a structure termed a capsule, the reality of which is being questioned. At any rate, when type I meningococci, any type of pneumococci or influenzae bacilli are mixed in a hanging drop preparation with the corresponding type-specific rabbit antiserum containing just enough methylene blue to make it lightly colored, the body of each organism stains deeply with the blue and is surrounded by a turbid grayish halo, sharply delineated by a

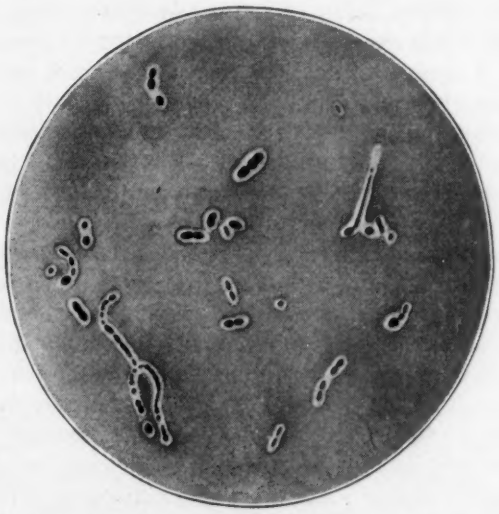

Fig. 1.—Typing of H. influenzae by capsular swelling with diagnostic typing serum.

well defined periphery. This halo has been called the capsule and the phenomenon termed capsular swelling. Figure 1 demonstrates these points. In each instance, during active growth of the organism a polysaccharide is released into the surrounding substrate in which the organism is multiplying. Each organism elaborates an antigenically individual polysaccharide which dissolves readily in body fluids. It is this substance which distinguishes one type from another within the species, as, for example, type I from type II pneumococcus and type a from type b H. influenzae. The identification of these substances through the phenomenon of capsular swelling also serves to eliminate confusion arising from pleomorphism of H. influenzae and poor staining with Gram stain by supplying proof that a given organism is a pneumococcus, a meningococcus or a strain of H. influenzae. During infections the concentration of these substances in the body fluids is an index to the severity and therefore determines the amount of antibody necessary for its neutralization and recovery from the infection. The evidence indicates that in each of these infections the protective element in therapeutic serum is the antibody to the specific carbohydrate. Furthermore, there is reason to believe that in

recovery from H. influenzae and meningococcic infections, as well as from those due to pneumococci, antibody, whether supplied by natural means or as the result of therapy with a sulfonamide compound or with serum, is an essential part of the process of recovery.

The signs which influence the physician to suspect inflammation of the meninges are conditioned to a large extent by the age of the patient and the duration of meningitis. In the age group beyond early infancy signs of meningeal irritation become manifest early. Here it is possible to describe the signs which the examiner sees at various stages. When the process is early, he sees only transient delirium, drowsiness, generalized hyperesthesia, hyperactive reflexes, definite resistance and pain on flexion of the neck and positive Kernig and Brudzinski reflexes.

After forty-eight hours, if the patient is untreated, the drowsiness passes into stupor, the back becomes rigid and retraction of the neck occurs. At this stage the thighs are flexed on the abdomen. Signs of increased intracranial pressure appear. Vomiting becomes a problem; the stupor deepens, and signs of involvement of the cranial nerves develop, followed frequently by evidence of localized cerebral involvement. In the young child the sutures separate; the head enlarges.

In infants under 7 months of age it is the perception of meningeal involvement which constitutes the chief problem. The patient's failure to manifest clear-cut signs of meningeal irritation until several days after onset presents a serious diagnostic difficulty and adds to the therapeutic problem. Successful treatment depends in large measure on early application of effective measures. Even under present conditions, since the advent of therapy effective against these forms of meningitis in older children, a large proportion of these young infants die. Evidence suggests that the advanced stage of the disease and the presence of irreparable damage at the time therapy is started are responsible for the high death rate. In any individual case searching inquiry almost invariably discloses the fact that unexplained fever had been present several days prior to any suspicion of meningitis. These considerations should lead one to reappraise the criteria for the recognition of meningeal disease in this age group. When the fontanel of a well hydrated infant is widely open and its tension is tested, experience enables one to detect an increase in intracranial pressure some time before stiffness of the neck or a positive Kernig sign is found. In fact, the latter signs are highly unreliable in the first few months of life, for they seldom appear before the advanced stage of meningitis. If the fontanel is not open sufficiently for an estimation of tension, the signs of meningeal involvement are frequently limited to drowsiness alternating with pronounced irritability, a high-pitched cry and a vacant look in the eyes. It is warranted to appeal for more frequent use of lumbar puncture when unexplained fever is accompanied by any suggestion of these features.

It is apparent from the description that a diagnosis more specific than inflammatory process of the meninges is impossible, for the potential agents are numerous and their manifestations nonspecific. Diagnosis must await examination of the spinal fluid. Table 1 gives the differential diagnostic features.

From the table it may be seen that the combination of the character of cell response and the chemical features of the spinal fluid provides a great deal of aid in delimiting the group of infections of the central nervous system. When there is a great predominance of lymphocytes and the dextrose and chloride levels of the spinal fluid are normal, it is probable that the infection is caused by a virus. A similar response of the spinal fluid is produced by lead encephalitis, but it differs in that the quantity of protein present is increased out of proportion to the number

of cells present. Tuberculous meningitis is in a class by itself, producing a lymphocytic response and decrease in the content of dextrose and chlorides. When polymorphonuclear cells predominate and the dextrose and chlorides are normal, the infection may be an early bacterial meningitis or sympathetic meningitis, the response to an infection contiguous to the meninges, the causative agent of which has not invaded the subarachnoid space. When the sugar and chlorides are decreased in amount and the cell response is polymorphonuclear, it must be assumed that a pyogenic organism is the responsible agent. It is important to recognize that the changes in the spinal fluid presented for the various varieties of infection of the central nervous system are the classic ones. They are typical of most patients and therefore serve as a useful guide. The predominance of polymorphonuclear cells found early in the course of equine encephalitis and occasionally in poliomyelitis are notable exceptions to the usual virus response just described.

Determination of the specific pyogenic agent can be accomplished only by bacteriologic and immunologic methods. Since early recognition and identification of type are essential for adequate treatment of pneumococcic and H. influenzae meningitis in children, rapid methods of diagnosis are of great importance. If organisms are sufficiently numerous to be demonstrable by stained smears of the

TABLE 1.—*Differential Diagnostic Features of the Spinal Fluid*

	Cell Response		Chemistry			
	Polymorphonuclears	Lymphocytes	Sugar	Chlorides	Protein	Identification
Virus infections	..	+	0	0	+	Animal infection
Lead encephalitis	..	+	0	0	++	Chemical and roentgen examination
Tuberculous meningitis	..	+	+	+	+	Culture and smear
Sympathetic meningitis	+	..	0	0	+	Culture
Mild pyogenic meningitis	+	..	0	0	+	Culture
Other pyogenic meningitis	+	..	+	+	+	Direct typing

spinal fluid or sediment obtained after centrifuging for twenty minutes at high speed the species and the type may be identified within a period of half an hour. The morphology and Gram-staining characteristics enable an experienced observer to differentiate the pneumococcus, the meningococcus and H. influenzae. However, the pronounced pleomorphism of H. influenzae, together with poor gram-staining properties, is frequently responsible for confusion which leads to serious delay in institution of specific antibody treatment. Moreover, there are no reliable morphologic features which distinguish H. influenzae from the various gram-negative bacilli which ordinarily inhabit only the intestinal tract but which not infrequently invade the meninges. It is clear that the capsular swelling phenomenon is of great value in determining the species as well as the specific type of the organism. Therefore, laboratories of hospitals admitting patients with any variety of meningitis should be equipped with pneumococcus, meningococcus and H. influenzae type-specific diagnostic serums.

The accumulated evidence on efficiency of sulfonamide compounds alone in treatment of pyogenic meningitis has been well reviewed by Dingle and Finland.[1] This may be summarized briefly. The sulfonamide compounds have produced brilliant success in treatment of sporadic meningococcic meningitis. Promising results have been obtained in the patients treated during the increased incidence of

1. Dingle, J. H., and Finland, M.: Diagnosis, Treatment, and Prevention of Meningococcus Meningitis, with Résumé of Practical Aspects of Treatment of Other Acute Bacterial Meningitides, War Med. **2**:1 (Jan.) 1942.

the disease in England, with exception of infants under 1 year; in the latter the mortality has been 50 per cent. The death rate varied between 22 and 24 per cent in 12,000 patients of all ages during 1940. There is general agreement that, provided epidemic experience does not change the present view, every patient should be treated with a sulfonamide compound alone unless the patient fails to respond or tolerate the drug. The degree of susceptibility of meningococci to the chemical agents probably exceeds that of most other bacteria. A low concentration of drug is therefore frequently effective; nevertheless it is advisable to administer 0.1 Gm. per kilogram of body weight intravenously as the initial dose and to maintain a blood level around 10 mg. per hundred cubic centimeters for the first forty-eight hours. All sulfonamide compounds in common use are effective.

A study of 3 patients recovering from meningococcic meningitis after treatment with a sulfonamide compound suggests that antibodies formed by the host in response to the infection play a part in the recovery process. Experimental work[2] suggests that a combination of specific antibody and a sulfonamide compound is more effective against lethal infections in animals than either agent alone. These results, together with the 50 per cent mortality in infants and the 24 per cent gross death rate, suggest that there are still indications for the use of serum. Rabbit serums, monovalent type I and polyvalent, standardized by quantitative methods are now available.

Unless striking improvement, as judged by the patient's clinical status and a change in the spinal fluid toward the normal, is apparent after forty-eight hours of treatment with sulfadiazine, rabbit serum should be administered intravenously. Its sufficiency should be checked by the methods already described.

While the mortality in pneumococcic meningitis of adults has been significantly reduced by the use of sulfonamide compounds alone, recoveries of children under 3 years following chemotherapy alone are rare.

Experience in a number of institutions casts a great deal of doubt on the figure of 35 per cent mortality arrived at by summary of the reported cases with treatment by a sulfonamide compound alone.[3] Here again, it is presumed that the publication of favorable results does not do justice to the picture as a whole. In Boston, the results still show a mortality of 80 per cent, even after all available agents were applied.[1]

Investigations of the immunologic aspects of the pneumococcus indicate that type-specific antibody is an essential part of the natural recovery mechanism as well as of that following use of a sulfonamide compound.[4] Treatment of experi-

2. (*a*) Branham, S. E., and Rosenthal, S. M.: Studies in Chemotherapy: V. Sulfanilamide, Serum and Combined Drug and Serum Therapy in Experimental Meningococcus and Pneumococcus Infections in Mice, Pub. Health Rep. **52**:685 (May 28) 1937. (*b*) Brown, T. M.: Protective Action of Sulfanilamide and Antimeningococcus Serum on Meningococcus Infection of Mice, Bull. Johns Hopkins Hosp. **61**:272 (Oct.) 1937.

3. (*a*) Coleman, F. H.: Pneumococcus Meningitis Since the Introduction of M & B 693, Lancet **2**:615, 1940. (*b*) Turnoff, D.; Marenus, E. B., and Schnabel, T. G.: Pneumococcus Meningitis with Reference to Sulfapyridine Therapy, Pennsylvania M. J. **44**:172, 1940. (*c*) Steele, C. W., and Gottlieb, J.: Treatment of Pneumococcus Meningitis with Sulfanilamide and Sulfapyridine: A Statistical Study of All Reported Cases in Which Chemotherapy Was Used, With or Without Specific Antipneumococcus Serum, Arch. Int. Med. **68**:211 (Aug.) 1941. (*d*) Hewell, B. A., and Mitchell, G. A.: The Treatment of Pneumococcus Meningitis with Sulfanilamide, J. A. M. A. **112**:1033 (March 18) 1939. (*e*) Gilmore, G. B., and Sacks, P.: Pneumococcus Meningitis: A Review of the English Literature with a Report of Two Cases in Which the Disease Was of Otitic Origin, Arch. Otolaryng. **32**:1007 (Dec.) 1940.

4. Curnen, E. C., and MacLeod, C. M.: Effect of Sulfapyridine upon Development of Immunity to Pneumococcus in Rabbits: Review of Investigations on Human Antibody Response to Pneumococcus Pneumonia, J. Exper. Med. **75**:77 (Jan.) 1942.

mental type I meningitis in rats suggests that a combination of serum and a sulfonamide compound is superior to either agent alone.[5]

This evidence, together with the high mortality of pneumococcic meningitis, makes it mandatory for the physician to use both a sulfonamide compound and serum for all patients with this disease. Here, too, well standardized rabbit serum is available, and the principles already discussed for gaging the size of the original dose and its sufficiency after administration are applicable.

The following review will cover the treatment of the severe H. influenzae infections encountered in infants and children: meningitis, empyema with bacteremia in infants under 1 year of age, and obstructive infections of the respiratory tract. Experimental evidence has been presented for the conclusion that a combination of sulfadiazine and type-specific antibody is the treatment of choice.

MENINGITIS

H. influenzae type b ranks among the three most frequent causes of meningitis in children, even holding first place in many institutions at times when meningococcic infection is not prevalent in the surrounding community. The spontaneous mortality of meningitis due to H. influenzae type b varies from 92 to 100 per cent when all age groups are considered. In a group of 127 patients more than 2 years of age, the death rate was found to be 80 per cent.[6] Fothergill[7] reported that with the use of horse serum and complement in 200 cases, the mortality was still 84 per cent. Treatment with horse serum and complement combined with administration of a sulfonamide compound has produced extremely inconstant results, varying from 82 to 54 per cent mortality.[8] Instances of recovery have been reported when sulfanilamide, sulfapyridine, sulfathiazole or sulfadiazine has been used alone. However, for the reasons already stated, adequate clinical evidence for evaluating the efficiency of sulfonamide compounds alone is not available.

Details of Treatment of Meningitis.—The details of the therapeutic program suggested on the basis of the evidence presented have already been reported.[9] As soon as all material necessary for determination of the causative organism is obtained, sulfadiazine is administered intravenously. When type b H. influenzae is established as the infectious agent, a continuous intravenous infusion is set up. During the next four hours, in addition to more sulfadiazine, a large quantity of fluid (40 cc. per kilogram) is introduced, in an attempt to speed up urinary excretion of specific soluble substance. This is advised on the premise that a given quantity of antibody is more effective if utilized mainly against the

5. Gross, P., and Cooper, F. B.: Therapeusis of Experimental Type I Pneumococcic Meningitis in Rats: Comparative Therapeutic Results Obtained with Sulfanilamide, Serum, and Combination Therapy, Am. J. M. Sc. **198**:66 (July) 1939.

6. Wilkes-Weiss, D., and Huntington, R. W., Jr.: Treatment of Influenzal Meningitis with Immune Serum, J. Pediat. **9**:462 (Oct.) 1936.

7. Fothergill, L. D.: Hemophilus Influenzae (Pfeiffer Bacillus) Meningitis and Its Specific Treatment, New England J. Med. **216**:587 (April 8) 1937.

8. (*a*) Neter, E.: Observations on Children with Influenzal Meningitis Who Were Treated with Specific Serum, Sulfanilamide and Sulfapyridine, Arch. Path. **28**:603 (Oct.) 1939. (*b*) Aleman, R.: Influenzal Meningitis: Review of Recent Literature with Case Reports, New Orleans M. & S. J. **93**:25 (July) 1940. (*c*) Silverthorne, N., and Brown, A.: Influenzal Meningitis, J. Pediat. **16**:456 (April) 1940. (*d*) Lindsay, J. W.; Rice, E. C., and Selinger, M. A.: Treatment of Meningitis Due to Hemophilus Influenzae (Pfeiffer's Bacillus), ibid. **17**: 220 (Aug.) 1940. (*e*) Neal, J. M.; Applebaum, E., and Jackson, H. W.: Sulfapyridine and Its Sodium Salt in Treatment of Meningitis Due to Pneumococcus and Haemophilus Influenzae, J. A. M. A. **115**:2055 (Dec. 14) 1940.

9. Alexander, H. E.; Ellis, C., and Leidy, G.: Treatment of Type Specific Hemophilus Influenzae Infections in Infancy and Childhood, J. Pediat. **20**:673 (June) 1942.

carbohydrate in the capsules of the organisms. Inhibition by chemotherapy should prevent the further liberation of large amounts of free carbohydrate into the blood and spinal fluid. In addition to affording the most efficient use of a given amount of antibody, this procedure for speeding up excretion of free specific carbohydrate should prevent the violent reactions of the severe forms of meningitis when a large quantity of antibody is given at one time. At the end of the first four hour period, the rabbit antibody is injected. The dose will be discussed later. The antibody, diluted in an amount of Ringer's solution or of physiologic solution of sodium chloride equivalent to 10 cc. per kilogram of the patient's body weight, is added to the reservoir of the continuous infusion, and the speed is adjusted so that the administration of diluted antibody is completed within two hours. At the end of the first twenty-four hours of treatment, the patient will have received large quantities of fluid by vein. The blood level of sulfadiazine will have been maintained by parenteral administration, and presumably he will have received enough antibody to establish an excess after neutralization of all antigen present. The recommended amount is intended to provide in a single dose the quantity of antibody necessary to accomplish this result.

As described previously, the level of the spinal fluid sugar before treatment reflects the severity of infection. The dosage of antibody is recommended on this basis, as shown in table 2.

TABLE 2.—*Schedule of Dosage Based on Dextrose Content of Spinal Fluid*

Spinal Fluid Sugar, Mg. per 100 Cc.	Antibody Nitrogen Indicated, Mg.
<15	100
15 to 25	75
25 to 40	50
Over 40	25

Twelve hours after the administration of the dose considered on the basis of the laboratory examination to be sufficient for recovery, the temporary adequacy of treatment is tested by examining the patient's serum for its ability to produce capsular swelling of a suitable suspension of H. influenzae. This procedure has been described. When satisfactory excess of antibody is not demonstrable, an additional dose equivalent to 25 mg. of antibody nitrogen is given and the serum retested a few hours later. A good degree of correlation has been found between the results of capsular swelling capacity of the patient's serum and the polysaccharide cutaneous test. However, my experience with the latter is not large enough to justify recommending it as the sole method for appraising excess of antibody.

In following the progress of our patients, we have been guided to a large extent by the changes developing in the spinal fluid; for a time we examine the fluid daily. If within twenty-four hours the sugar and chlorides have risen, no organisms are seen on direct smear and the patient's serum causes capsular swelling when diluted 1:10, no further antibody is needed, provided all these elements continue to progress toward their normal level, the cultures become and remain sterile and antibody persists in the serum in adequate excess. In all infections it is our policy to limit administration of serum to the intravenous route for a period of forty-eight hours after the institution of antibody therapy. If at the end of this period evidence of satisfactory progress is lacking, a dose equivalent to 25 mg. of antibody nitrogen should be administered intrathecally.

After sulfadiazine has been given parenterally for twenty-four hours and the patient appears better, 0.1 Gm. per kilogram is administered daily by mouth, and the dose is continued for seven days after the spinal fluid is first shown to be sterile.

Some hospitals are not equipped to carry out this therapeutic program. Under such circumstances, it is wise whenever possible to transport children with meningitis to a pediatric institution well equipped for handling these problems. Failing that, the original spinal fluid should be sent off immediately on withdrawal by air mail if the distance warrants, to a pediatric hospital laboratory. During the interval necessary for identification of the organism sulfadiazine should be administered in dosage sufficient to maintain a blood level of the drug of 15 mg. per hundred cubic centimeters. If attempts to administer the drug intravenously meet with failure, a 5 per cent solution of the sodium salt may be injected subcutaneously at intervals of twelve hours. The details of this mode of treatment have been reported recently by Jorgensen and Greeley.[10] The fluid requirement of the child may also be met by the subcutaneous route when necessary. For the present, the administration of antibody by other than the intravenous course is not recommended. A study of the rate of absorption from intramuscular areas is planned.

Results.—Thus far we have records of 75 patients with H. influenzae meningitis treated with a combination of a sulfonamide compound and specific rabbit anti-

TABLE 3.—*Route of Administration of Serum, with Results, in Treatment of H. Influenzae Meningitis*

	Number of Cases		
	Total	Recovered	Fatal
Intravenous only	34	32	2
Intravenous + intrathecal	41	25	16
	75	57	18

serum. Table 3 presents results of the two variations in route of therapy; namely, when antibody was used both intravenously and intrathecally and when it was limited to the intravenous route. To 41 of the 75 patients antibody was administered both intrathecally and intravenously; to 34, by the intravenous route only. The high recovery rate in the group treated by the intravenous route alone is somewhat misleading, since failure to respond in forty-eight hours was followed by intrathecal administration of serum in addition. With 1 exception, this has been necessary only for patients in whom the infection had already reached the chronic stage, when rabbit antibody was used. On the basis of our experience, intravenous treatment alone not only is justified but is considered the route of choice for all patients initially.

When serum was given by vein alone, the spinal fluid became sterile just as rapidly as when serum was injected intrathecally in addition. The increased meningeal inflammation due to introduction of foreign protein into the subarachnoid space was eliminated. Discomfort caused by treatment was greatly reduced.

Figure 2 represents the course of an infant treated according to the old regimen. Rabbit serum was administered both intravenously and intrathecally daily for four days and by the intrathecal route only for another two days. The latter route

10. Jorgensen, G. M., and Greeley, D.: Subcutaneous Administration of Sodium Sulfadiazine, J. Pediat. **21**:325 (Sept.) 1942.

was used daily for injection of serum until two consecutive samples of spinal fluid were shown to remain sterile for forty-eight hours. This is a good example of the marked increase in clinical signs of meningitis, the high sustained fever and the increase in cells and protein in the spinal fluid, which may be produced by intrathecal administration of serum. This was the second patient to be treated with rabbit serum, and the quantitative approach had not yet been worked out. At the

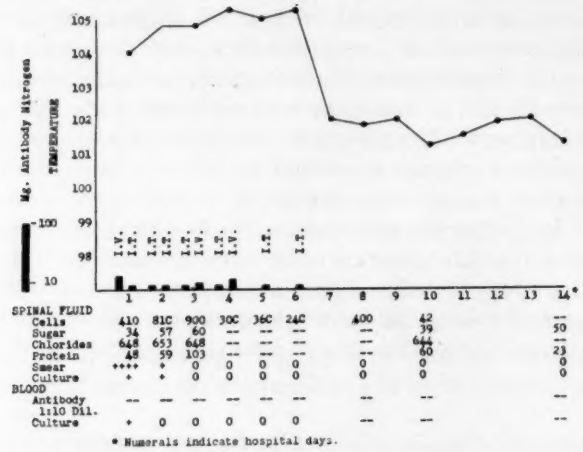
Mg. Antibody Nitrogen
TEMPERATURE
I.V. I.T. I.T. I.T. I.V. I.T. I.V. I.T. I.T.
1 2 3 4 5 6 7 8 9 10 11 12 13 14*
SPINAL FLUID
Cells 410 810 900 300 360 240 400 42 --
Sugar 34 57 60 -- -- -- -- 39 50
Chlorides 648 653 648 -- -- -- -- 644 --
Protein 48 59 103 -- -- -- -- 60 23
Smear ++++ + 0 0 0 0 0 0 0
Culture + + 0 0 0 0 0 0 0
BLOOD
Antibody 1:10 Dil. -- -- -- -- -- -- -- -- --
Culture + 0 0 0 0 0 -- -- --
* Numerals indicate hospital days.

Fig. 2.—Temperature and laboratory data for W. W., aged 1 year. Sulfanilamide was administered for seven days. *I.V.* indicates intravenous administration of serum and *I.T.* intrathecal administration.

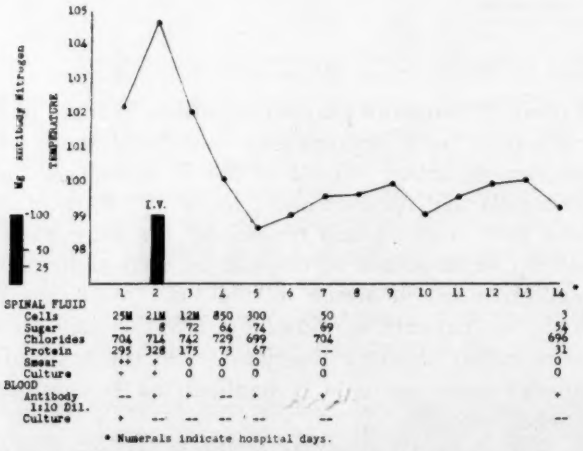
Mg Antibody Nitrogen
TEMPERATURE
I.V.
1 2 3 4 5 6 7 8 9 10 11 12 13 14*
SPINAL FLUID
Cells 25M 21M 12M 850 300 50 3
Sugar -- 8 72 64 74 69 54
Chlorides 704 714 742 729 699 704 696
Protein 295 328 175 73 67 -- 31
Smear ++ + 0 0 0 0 0
Culture + + 0 0 0 0 0
BLOOD
Antibody 1:10 Dil. -- + + -- + + +
Culture + -- -- -- -- -- --
* Numerals indicate hospital days.

Fig. 3.—Temperature and laboratory data for D. H., aged 3 years. Sulfanilamide was administered for eight days.

beginning of the second week signs of serum sickness developed, which appeared to be the only cause of the temperature of 101 to 102 F. over a period of two weeks. During this time the child appeared well and the spinal fluid remained normal with exception of a cell count of 40 lymphocytes per cubic millimeter.

Figure 3 exhibits the characteristic response of a child who was treated within twenty-four hours of the onset of illness with sulfanilamide and rabbit antibody by the intravenous route, according to the method described. It is of interest

that this patient, who showed signs (according to laboratory and clinical criteria) of an extremely severe infection, responded to treatment just as dramatically as those exhibiting a milder form of the disease. Early initiation of specific treatment appears to be very important for such patients.

Figure 4 demonstrates the course of a patient who first received rabbit antibody after twenty-eight days' treatment with sulfapyridine and horse serum which had been administered daily by the intrathecal route. On admission to the Babies Hospital the patient presented a classic picture of chronic meningitis. It was therefore surprising that he was clear mentally. A bilateral tremor was present, suggesting some encephalitis. As the chart shows, his course was stormy despite the fairly prompt response of culture and chemical constituents of the spinal fluid. It was not surprising, therefore, that H. influenzae was grown from the spinal fluid after a period of twelve days of sterile cultures. Since adequate antibody had been maintained in the blood throughout this period, it appeared that antibody administered intrathecally might contribute some additional benefit. Thereafter improvement was rapid.

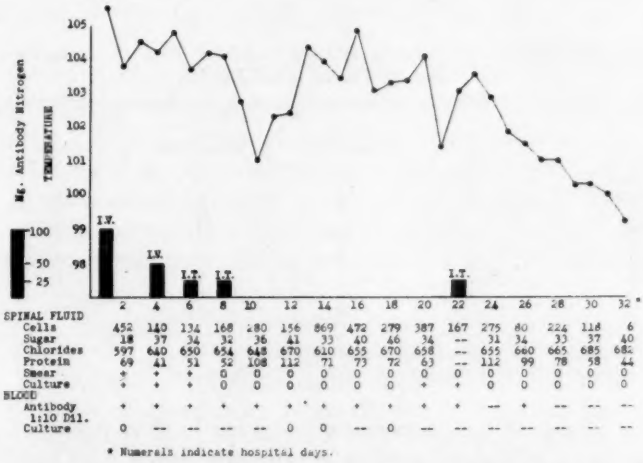

Fig. 4.—Temperature and laboratory data for R. G., aged 3½ years. Sulfanilamide was administered for thirty-five days. *I. V.* indicates intravenous administration of serum and *I. T.* intrathecal administration.

TABLE 4.—*Summary of Results by Years of Combining Rabbit Antibody and Chemotherapy in Treatment of H. Influenzae Meningitis*

Year	Recoveries		Fatalities		Total
	No.	%	No.	%	
1938-1939	8	57	6	43	14
1940	15	75	5	25	20
1941	14	88	2	12	16
1942	18	80	4*	20	22
1943	2	66	1	33	3
	57	76	18	24	75

* Three patients were treated with sulfonamide compounds for three weeks in other institutions prior to the administration of rabbit serum.

The program of treatment is effective. Table 4 summarizes our therapeutic results by years. During the period of 1938-1939 the patients were treated with unconcentrated rabbit serum made at the Babies Hospital. Squibb's concentrated

antibody solution, produced and assayed according to our specifications, was used for all other patients. The evidence indicates that the improvement in results over this four year period is due chiefly to a more efficient application of the quantitative approach. It has not been due to a more favorable age distribution of patients.

Table 5 shows the incidence with relation to age and the results of therapy in the different age groups. It demonstrates what has been emphasized previously, that the unsatisfactory therapeutic result obtained with infants under 7 months of age constitutes the greatest problem. All evidence indicates that the high mortality in infants under 7 months of age is due to the advanced character of the disease at the time signs diagnostic of meningitis become manifest. For improvement in results at this age, one must depend on improved clinical perception.

With 1 exception recovery has been complete in all children included in this series who survived. This child, whose clinical features suggested an encephalitic component, had bilateral retinal hemorrhages. Visual acuity was greatly decreased, but within six months after recovery from meningitis her vision was grossly normal.

TABLE 5.—*Age Distribution of Patients Who Recovered from H. Influenzae Meningitis and of Those Who Died*

Age	Total Number	Recovered	Died	Per Cent Recovery
3 to 7 months	9	2	7	22
7 to 12 months	11	9	2	82
1 to 2 years	19	17	2	89
2 to 3 years	20	15	5*	75
3 to 4 years	6	5	1	83
4 to 5 years	7	7	0	100
Over 5 years	3	2	1	66
	75	57	18	74†

* In 2 cases leukopenia; in 2 cases insufficient treatment.
† Average percentage of recovery of patients over 7 months of age 82.

In the early phase of the therapeutic program lumbar puncture is performed daily; this precaution is discontinued only after the spinal fluid has become sterile and the chemical and cellular aspects of the spinal fluid have approached normal. We have seen recurrence of infection after the original sterilization of the spinal fluid only when persistent leukopenia develops and in instances in which the meningitis had assumed a chronic form before rabbit serum was used. As a measure of safety all patients are kept in the hospital for one week after signs of recovery have appeared. After this state of apparent recovery has materialized, we have seen several patients who showed a return of fever and increase of cells and protein in the spinal fluid. The spinal fluid was sterile on culture, and the concentration of sugar and chlorides remained normal. Signs of serum sickness, in some instances meager, accompanied this change in the spinal fluid. Although at the onset of this situation it is impossible to recognize the cause before the results of culture are known, our experience includes a number of patients who continued to have sterile spinal fluid and whose spinal fluid cells and protein all returned to normal in a few days. It is believed that these episodes represent localized reactions of the meninges to the serum. Resumption of chemotherapy is justified under these circumstances until the nature of the meningeal reaction is determined. On the other hand, additional injections of rabbit serum should be resorted to only when organisms are again identified directly in the spinal fluid or in cultures by the capsular swelling method.

PNEUMONIA AND EMPYEMA WITH BACTEREMIA IN INFANTS UNDER 1 YEAR OF AGE

The unfavorable outlook for infants with this variant of the infection justifies the use of type-specific antibody as soon as empyema with bacteremia due to type b H. influenzae is recognized. By the time these infants reach the hospital, the empyema is often well established and the organisms may be identified directly from the pleural fluid. In other instances the positive blood culture gives the first indication of the cause, the baby having been treated for pneumonia with a sulfonamide compound without response.

Because of the frequent development of meningitis following empyema with bacteremia and the difficulty experienced in recognizing its presence in young infants, we have adopted the policy of performing lumbar puncture in all such cases. If meningitis is shown to be present, it is treated in the manner already described. If the meninges are not yet involved, a dose of antibody equivalent to 50 mg. of antibody nitrogen is given initially by intravenous injection and its sufficiency checked within a few hours. Aspiration of pleural fluid is practiced when necessary to relieve respiratory embarrassment.

OBSTRUCTIVE INFECTIONS OF THE RESPIRATORY TRACT

It has been asserted that a single agent, presumably a virus, is the sole cause of all nondiphtherial infections which obstruct breathing by producing inflammatory stenosis of the larynx alone or in combination with other portions of the bronchial tree. There is no evidence in favor of this view. Moreover, regardless of what prepares the way, it seems clear from our experience that the major pathologic changes are due to invasion by one or another of a number of different pyogenic bacteria.

The syndrome of laryngotracheobronchitis was first attributed to H. influenzae in 1936 by Lemierre.[11] In 1940 the general features of respiratory obstructions produced by H. influenzae infection were described.[12] Recently Sinclair [13] has reported on a group of cases from New Haven, Conn., and has described their characteristic clinical features in detail. Our experience at the Babies Hospital parallels his in every respect. The agency of H. influenzae in this disease will escape recognition unless the blood is cultured, since routine cultures of materials from the nose, throat and larynx alone usually fail to isolate this organism unless there is special interest in looking for it. It is believed that this is probably not an unusual disease, though it occurs less frequently than H. influenzae meningitis.

When H. influenzae type b is responsible for an obstructive laryngeal, laryngotracheal or laryngotracheobronchial infection, the illness presents a characteristic history and the patient a characteristic appearance. The onset is sudden and the course fulminating. The entire length of acute illness in those cases which terminate fatally is usually less than twenty-four hours. Mild fever and difficulty in swallowing and complaint of sore throat on the part of the older children make their appearance in the course of an apparently innocuous infection of the upper respiratory tract. Dyspnea starts abruptly and increases within a few hours to such a degree as to make hospitalization imperative. The characteristic picture is that

11. Lemierre, A.; Meyer, A., and Laplane, R.: Les septicémies à bacille de Pfeiffer, Ann. de méd. **39**:97 (Feb.) 1936.

12. Holt, L. E., Jr., and McIntosh, R.: Holt's Diseases of Infancy and Childhood, ed. 11, New York, D. Appleton-Century Company, Inc., 1940.

13. Sinclair, S. E.: Haemophilus Influenzae Type b in Acute Laryngitis with Bacteremia, J. A. M. A. **117**:170 (July 19) 1941.

of a prostrated child with dyspnea due to laryngeal obstruction. The temperature is high. Effort on the part of the child to increase the airway produces a dramatic scene, which in some cases takes the form of forcible protrusion of the tongue with each inspiration; other patients hold the mouth widely open during both inspiration and expiration. On examination of the pharynx there is diffuse erythema, often with evident edema, and when the tongue is pressed downward the enlarged red and edematous epiglottis is easily seen. Direct laryngoscopic examination shows almost complete approximation of the posterior wall of the epiglottis to the swollen arytenoepiglottic folds. The vocal cords are usually uninvolved, and the voice is not impaired. At times the cervical lymph nodes are enlarged. Usually the obstruction of breathing is due almost exclusively to edema of the epiglottis and other supraglottic structures. Hence, the process should be termed laryngitis with epiglottitis and not laryngotracheobronchitis, a term frequently used loosely, unless there is evidence that the process extends well into the bronchi. The obstructive syndrome described has been found in our experience only in association with type b H. influenzae infection, and therefore when observed suggests such infection immediately. Bacteremia appears to be a constant feature. Occasionally when the infection extends into the trachea, bronchi and bronchioles, bronchopneumonia ensues; this is the severest form of the disease.

Treatment of Infections Which Produce Obstruction of the Respiratory Tract.— In these critically ill patients one is faced with two problems: relief of obstruction to respiration and treatment of the local infection and bacteremia.

Tracheotomy is frequently imperative within a few hours after onset of dyspnea. For other patients, when this procedure is not obviously urgent, exact criteria for intervention are controversial even among physicians with most experience. Sudden complete obstruction following manipulation inside or outside the respiratory tract is seen not infrequently. For this reason a bronchoscope, the Mosher life saver or some comparable device to maintain an open airway is a necessary part of the equipment for handling these patients prior to tracheotomy. Only 3 patients, 15 per cent of the combined series to be presented, recovered without tracheotomy. One of these patients was 11 years old. Since the probability of the need for tracheotomy is so great and the risk of delaying too long is so hazardous, early operation, while circumstances are still favorable, is strongly advised. It is difficult to define the term "early" as it is used here. Certain points are obvious, however. One aims to perform a tracheotomy as soon as it becomes clear that the degree of obstruction is progressive and before the child becomes exhausted. Only judgment based on experience can determine these phases.

Rapid identification of the causative organism and determination of the severity of the infection are essential for effective therapy for some patients. Strong presumptive evidence of the responsible agent is obtained when direct examination of nasopharyngeal mucus reveals the presence of type b H. influenzae by the capsular swelling method. Further confirmation is obtained when the mucus from the trachea after tracheotomy is shown to harbor the same organisms. In many cases the ultimate proof must await demonstration of bacteremia. However, in the most severe infections the final proof of cause as well as an immediate index of severity may be contributed by demonstrating the presence of type-specific carbohydrate in the patient's serum by means of the precipitin test described.

Immediately after the physical examination and collection of the specimens indicated, an infusion of sulfadiazine (0.1 Gm. per kilogram) is given and a continuous intravenous infusion set up. Subsequent chemotherapy follows the schedule described under the section on meningitis.

Since some of these patients respond promptly to sulfonamide compounds alone, the essential problem at present is to select those to whom administration of antibody in addition is probably essential for recovery. A crude estimate of the concentration of type-specific carbohydrate present in the patient's serum is of value in gaging the severity of the disease.

To patients who show a positive precipitin reaction within ten minutes after the test is set up, it is our custom to give an amount of type b H. influenzae rabbit antibody which contains 50 mg. of antibody nitrogen. The concentrated serum, diluted as previously described, is added to the continuous infusion after the first four hour period during which sulfadiazine and fluids have been administered. The adequacy of the dose is checked by examining the patient's serum for excess of free antibody by the capsular swelling method. If the patient shows extension of the inflammatory process into the finer bronchi, as evidenced by failure of tracheotomy to relieve the respiratory obstruction, we believe that this alone constitutes an indication for antibody. The need for antibody therapy for all other patients with a negative reaction for specific soluble substance must be judged by the patient's response to a sulfonamide compound over a period of twenty-four hours.

TABLE 6.—*Results of Treatment Used at the Babies Hospital and New Haven Hospital for H. Influenzae Infections Causing Obstruction of the Respiratory Tract*

Treatment Used	Results		
	Recoveries	Fatalities	Total
Tracheotomy, no specific therapy	1	4	5
Tracheotomy + sulfonamide compound	6	0	6
Tracheotomy + sulfonamide compound + serum	5	0	5
Sulfonamide compound + serum, no tracheotomy	1	0	1
Sulfonamide compound only, no tracheotomy	2*	0	2
No treatment	0	4	4
	15 (65%)	8 (34%)	23

* Ages of patients 11 years and 6 years.

An analysis of the results of treatment at the Babies Hospital and those at the New Haven Hospital, the latter published by Sinclair,[13] is shown in table 6. The effectiveness of the sulfonamide compounds combined with tracheotomy but without antibody is striking and warrants a trial for all but the most severe infections selected by the method described.

Table 7 presents the relevant data on our 13 cases of type b H. influenzae infections causing obstruction of the respiratory tract. It demonstrates the uniformity of the history and clinical features. All the patients were over 2 years of age. The onset of any indication of illness occurred less than twenty-four hours before the patient's admission to the hospital except in the case of the 11 year old boy, who had fever and sore throat for forty-eight hours. Dyspnea became severe so rapidly that all patients, except the 1 boy, were admitted to the hospital within a few hours of onset. Epiglottitis was a constant feature. In only 1 of the patients who recovered was the inflammatory process found to extend into the trachea and bronchi. In this patient, M. F., empyema developed early in spite of the use of sulfanilamide and sulfapyridine and the bacteremia continued over a period of three weeks. After a febrile course of five weeks, she finally recovered after rib resection.

Only 4 patients have been treated since the institution of the therapeutic program outlined. All had classic examples of the syndrome with epiglottitis and with

evidence that all obstruction was supraglottic. The response of these patients is shown in table 8.

This limited experience suggests that the test used for estimating concentration of polysaccharide is probably not sufficiently sensitive for the present purposes.

TABLE 7.—*Significant Data on Patients with Obstructive Lesions of Respiratory Tract Due to H. Influenzae*

Patient	Age, Yr.	Duration of Symptoms: Fever and Sore Throat, Hr.	Duration of Symptoms: Dyspnea, Hr.	Pathologic Changes: Epiglottitis	Pathologic Changes: Other Types	Culture of Blood	Treatment: Drug *	Treatment: Rabbit Serum	Treatment: Tracheotomy	Results
R. M.	2	4	4	+	0	+	S	+	+	Recovered
G. W.	4	12	6	+	0	+	S	+	+	Recovered
F. J.	4	24	3	+	Pneumonia; adenitis	+	S	+	+	Recovered
P. V.	3	24	6	+	0	+	D	+	+	Recovered
S. S.	8	12	5	+	0	+	P	0	+	Recovered
R. R.	11	48	24	+	0	+	S	0	0	Recovered
M. F.	5	?	3	+	L. T. B.;† empyema	+	S + P Surgical drainage	0	+	Recovered
F. O.	4	14	3	+	0	+	S	0	+	Recovered
A. C.	2	18	2	+	Periarticular abscess	+	0 Surgical drainage	0	+	Recovered
E. L.	2	12	6	+	L. T. B.; pneumonia	+	0	0	+	Died after 2 hr.
C. W.	10	8	5	+	Pneumonia; meningitis	0	0	0	+	Died after 3 mo.
J. E.	4	9	5	+	0	+ 0 col.	0	0	0	Died after 45 min.
E. H.	4	18	12	±‡	Pharyngeal cellulitis	+	0	0	0	Died after 2 hr.

* S indicates sulfanilamide; P, sulfapyridine, and D, sulfadiazine.
† L. T. B. indicates laryngotracheobronchitis.
‡ No examination of the larynx or epiglottis was made, but the child breathed in a manner characteristic of edema of the epiglottis.

TABLE 8.—*Application of the Therapeutic Program to Patients with Type b H. Influenzae Epiglottitis*

Patient	Age, Yr.	Period with Drug* Alone: Time Continued	SSS Test on Serum	Blood Culture (Colonies/Cc.)	Response to Serum: Clinical Improvement, Hours	Response to Serum: Temperature, F.	Extubation, Days After Admission
R. M.	2¼	S, 4 hours / 10 days	+	+ / 1	24	104 to 101, 24 hours	18
F. J.	5	S, 24 hours / 7 days	0	+ / 3	24	104 to 101- 24 hours	14
G. W.	4	S, 72 hours / 7 days	0	+ / 1	48	103.6 to 99.8, 36 hours	12
P. V.	3	D, 12 hours / D, 3 days S, 5 days	0	+ / 1	24	106 to 100.4, 24 hours	7

* S, sulfanilamide; D, sulfadiazine.

A treatment which brings about rapid subsidence of infection is desirable, because of the risk involved when complications occur. On the other hand, some of these patients might have recovered after treatment with a sulfonamide compound alone if given more time. Obviously, a larger series of patients must be treated according to these criteria before the program can be appraised.

CONCLUSION

I have tried to emphasize the complementary nature of the action between the sulfonamide compounds and type-specific antibody in their conquest of three types of meningeal infection. The greater the inhibitory influence of a sulfonamide compound the greater the consequence of antibody formation by the host. The susceptibility of the meningococcus to the action of such a drug justifies the use of sulfadiazine alone in this type of meningitis, unless the patient fails to show a prompt response. However, the death rate which still prevails during its epidemic occurrence should lead one to follow closely the progress of each infection for evidence of the patient's need for more antibody than he can produce. There is reason to believe that this adjunct is necessary only for some of the young infants and for patients of other age groups with overwhelming infections. In vitro experiments show the limitation of chemotherapeutic agents when the inoculum exceeds certain bounds and raises the possibility that a similar deficiency of the sulfonamide compound is operating in overwhelming infections.

On the basis of experience with H. influenzae meningitis, the intravenous route alone is recommended for administration of antibody in all three varieties of meningitis.

An occasional patient with pneumococcic and H. influenzae meningitis recovers after use of a sulfonamide compound alone when treatment is started early in the course of a mild infection. The inhibitory action in the test tube and the protective power in mice demonstrate the efficiency of these agents. However, the evidence based on investigation of the biologic features of the organisms, on experimental work on animals and on results in the treatment of these infections in children suggests that the ideal treatment combines specific antibody with sulfadiazine. This will probably suffice for all degrees and stages of pneumococcic and H. influenzae meningitis. Application of the quantitative approach will guide one in keeping the dose to a minimum. Moreover, even in cases in which the infection is judged mild by laboratory criteria and in which recovery may be expected with use of a sulfonamide compound alone, administration of small doses of antibody nitrogen, say 25 mg., supplemented by small increments, about 25 mg., when indicated on the basis of insufficiency of the preceding dose, should decrease the risk of therapeutic failure.

3575 Broadway.

News and Comment

GENERAL NEWS

Recommendation for Action in Epidemics of Poliomyelitis.—The Committee on Therapeutic Procedures for Acute Infectious Diseases and on Biologicals of the American Academy of Pediatrics reports the following recommendation: "The wisest course is to postpone elective operations on the nose and throat during epidemics of poliomyelitis."

Abstracts from Current Literature

Metabolism; Infant Feeding; Milk and Other Foods

DIGESTIBILITY AND BIOLOGICAL VALUE OF WHOLE WHEAT BREADS AS COMPARED WITH WHITE BREAD. JOHN R. MURLIN, MARGARET E. MARSHALL and CHARLES D. KOCHAKIAN, J. Nutrition **22**:573 (Dec.) 1941.

Murlin, Marshall and Kochakian, using 10 healthy men as experimental subjects, noted that higher biologic values were produced from the whole wheat breads in their diet than from white bread. The whole wheat breads gave lower true digestibility values for the protein than the white. This proves the fallacy of the widely held opinion that highest digestibility of protein confers the greatest nutritive value. If the biologic value of egg proteins is taken as 100 per cent, the biologic values for the whole wheat foods studied were 77.8, 79.6, 81 and 81.6 per cent; for white bread, 75.3 and 74.6 per cent, and for white bread baked with "high vitamin yeast," 79.8 per cent.

From the standpoint of the biologic value of protein, bread should be made with "high vitamin yeast," or extra vitamins of the B complex should be included in the diet to improve biologic value.

FREDEEN, Kansas City, Mo.

APPARENT DIGESTIBILITY OF CARBOHYDRATES, FATS, AND "INDIGESTIBLE RESIDUE" IN WHOLE WHEAT AND WHITE BREADS. ROBERT R. SEALOCK, DANIEL H. BASINSKI and JOHN R. MURLIN, J. Nutrition **22**:589 (Dec.) 1941.

Sealock, Basinski and Murlin concluded that under the conditions of their experiments, in which the diet furnished adequate calories for maintenance of weight for each of 10 healthy men, the higher "indigestible residue" of the whole wheat products did not interfere with the digestion and absorption of carbohydrate and fat.

FREDEEN, Kansas City, Mo.

THE RELATIVE ASSIMILATION OF FLUORINE FROM FLUORINE-BEARING MINERALS AND FOOD (TEA), AND FROM WATER FOOD. MARGARET LAWRENZ and H. H. MITCHELL, J. Nutrition **22**:621 (Dec.) 1941.

By controlled feeding experiments on growing rats Lawrenz and Mitchell made comparisons of the retention of dietary fluorine from supplements of sodium fluoride, calcium fluoride, green tea and raw rock phosphate and from sodium fluorine administered in water and in food. In all experiments the fluorine was administered at levels sufficiently low to have significance comparable to that of the fluorine hazard in human nutrition. They concluded that the fluorine sodium fluoride was neither more assimilable nor more toxic than that in calcium fluoride. The fluorine in sodium fluoride was more assimilable (5 per cent) than that in green tea or raw rock phosphate. The fluorine of sodium fluoride was 21 per cent more completely assimilated when administered in drinking water than when the same amounts were consumed in foods.

FREDEEN, Kansas City, Mo.

THE DIET OF YOUNG INFANTS. CHARLES HENDEE SMITH, New York State J. Med. **41**:2395 (Dec. 15) 1941.

Smith says that the slightest hint from the mother that she wants the baby to be bottle fed is too often taken as grounds for weaning. Improvements in artificial food methods, indifference and mismanagement have caused a falling off in the percentage of breast-fed babies.

"Breast feeding is not a lost art, but its management is a real art. No obstetrician is justified in predicting whether a normal, healthy woman can nurse her baby until she has been given a fair trial. The nurse who interferes in the matter is stepping outside her province in a most unprofessional way. There is no single guide to the management of the feeding of any infant."

Mothers fear being kept from social engagements or from the companionship of their husbands. They also dread losing their figures. The old arguments in favor of breast feeding are interestingly presented. Breast feeding is still the routine method in the nurseries at Bellevue Hospital. Only 10 per cent of the babies receive any artificial food during the first ten days, and when they are returned to the outpatient department 85 per cent are still breast fed. In one nearby hospital only 10 per cent are still nursing in a similar time.

"I have never found a mother willing or able to increase the milk by manual stripping."

A review of artificial feeding is also given.

AIKMAN, Rochester, N. Y.

TRANSFUSION OF BOVINE SERUM ALBUMIN INTO HUMAN BEINGS. HARRY A. DAVIS, A. G. EATON and J. WILLIAMSON, Proc. Soc. Exper. Biol. & Med. **49**:96 (Jan.) 1942.

Previous experiments showed that the administration of bovine serum albumin was effective in raising and maintaining the blood pressure of dogs subjected to severe hemorrhage. When serum albumin was administered to 13 human subjects (15 to 65 years old) at the rate of 5 cc. per minute for a total of 50 to 300 cc., no untoward reactions were noted. The significance of bovine albumin as a substitute for blood for human beings is discussed.

HANSEN, Minneapolis.

DIETETICS AND DISEASE. BENITO SORIA, Bol. Inst. internac. am. de protec. a la infancia **15**:404 (Jan.) 1942.

The author considers that the most important protection with regard to health is that relating to public nourishment. He warns that the supplying of caloric needs is not sufficient, emphasizing the value of vitamins and minerals. Raw vegetables should have special preference in the diet, and all toxic drinks, condiments and exciting stimulants and the bad habit of eating quickly should be avoided. [EDITOR'S SUMMARY.]

Vitamins; Avitaminoses

A RIBOFLAVIN EXCRETION TEST AS A MEASURE OF RIBOFLAVIN DEFICIENCY IN MAN. VICTOR A. NAJJAR and L. EMMETT HOLT JR., Bull. Johns Hopkins Hosp. **69**:476 (Nov.) 1941.

One milligram of riboflavin was given intravenously to 10 normal subjects. In a four hour period from 32 to 72 per cent of the injected dose was retained in the body. In 4 subjects with induced riboflavin deficiency 81 to 93 per cent of the injected dose was retained.

LYTTLE, New York.

VITAMIN A DEFICIENCY AND INTESTINAL PERMEABILITY TO BACTERIA AND TOXIN. WALTER A. STRYKER and MARTHA JANOTA, J. Infect. Dis. **69**:243 (Nov.-Dec.) 1941.

Stryker and Janota made observations on the permeability of the intestinal wall to bacteria and toxins of rats deficient in vitamin A and in control animals, using a suspension of Salmonella enteritidis and toxin of Clostridium botulinum as test substances. No noteworthy differences between the two groups of rats were demonstrable.

TOOMEY, Cleveland.

DIFFERENCES IN THE BEHAVIOR OF RATS AND MICE TOWARDS DEFICIENCIES OF CERTAIN MEMBERS OF THE VITAMIN B COMPLEX. JOHN R. FOY and LEOPOLD R. CERECEDO, J. Nutrition **22**:439 (Nov.) 1941.

Foy and Cerecedo found that mice, unlike rats, did not develop the specific dermatitis usually associated with a lack of vitamin B_6. Pyridoxine added to their daily ration did not cause any growth response.

FREDEEN, Kansas City, Mo.

THE EFFECT OF INCUBATION ON THE VITAMIN CONTENT OF EGGS. ESMOND E. SNELL and ERNESTINE QUARLES, J. Nutrition **22**:483 (Nov.) 1941.

Snell and Quarles found that incubation did not change the total amount of pantothenic acid and riboflavin present in hen eggs. The amount of biotin remained constant or decreased. The chick embryo synthesized nicotinic acid and inositol.

FREDEEN, Kansas City, Mo.

THIAMINE, NICOTINIC ACID, RIBOFLAVIN, AND PANTOTHENIC ACID IN RYE AND ITS MILLED PRODUCTS. AARON J. IHDE and HENRY A. SCHUETTE, J. Nutrition **22**:527 (Nov.) 1941.

By microbiologic methods, Ihde and Schuette assayed samples of the products of the rye-milling process for components of the vitamin B complex, namely thiamine, nicotinic acid, riboflavin and pantothenic acid. The concentration of each of the vitamins was greatest in the germ, except for pantothenic acid, which was found more in the middlings. The flour contained approximately two thirds of the total vitamins, thus being a richer source of vitamins of the B complex than white wheat flour. Rye flour contains 50 per cent of its total vitamin content in the dark portion, which constitutes only a third of the total flour. Riboflavin possibly was the only vitamin lost by bleaching.

FREDEEN, Kansas City, Mo.

NICOTINIC ACID CONTENT OF MEAT AND MEAT PRODUCTS. J. M. McINTIRE, HARRY A. WAISMAN, LAVELL M. HENDERSON and C. A. ELVEHJEM, J. Nutrition **22**:535 (Nov.) 1941.

McIntire and co-workers determined the nicotinic acid content of meats by the cyanogen bromide–aniline method. The richest sources of nicotinic acid were liver and kidney. A significant amount of nicotinic acid was found in all animal tissue. Some loss of the vitamin occurred through cooking and commercial processing. FREDEEN, Kansas City, Mo.

METABOLIC STUDIES IN PATIENTS WITH GASTROINTESTINAL CANCER: III. THE HEPATIC CONCENTRATIONS OF VITAMIN A. JULES C. ABELS, ALICE T. GORHAM, GEORGE T. PACK and C. P. RHOADS Proc. Soc. Exper. Biol. & Med. **48**:488 (Nov.) 1941.

No essential difference was found in the vitamin A content of the livers of 21 adult control subjects and 14 patients with cancer (13 gastric and 1 colon). From this it would appear that the abnormally low level of vitamin A of the plasma in 85 per cent of the patients with gastrointestinal cancer is not due to decreased capacity of the livers of these patients to store vitamin A. HANSEN, Minneapolis.

ARE SEASONAL VARIATIONS OF SOME DISEASES RELATED TO THE VITAMIN CONTENT OF THE FOOD? NILS ALWALL, Nord. med. (Hygiea) **12**:2904 (Oct. 11) 1941.

The incidence of catarrhal diseases in Denmark and Sweden increases during the vitamin-rich months of the autumn, attains its highest peak at the new year and decreases during the late winter and early spring months, although the supply of vitamins then rapidly decreases. WALLGREN, Göteborg, Sweden.

THE VITAMIN A REQUIREMENT OF INFANTS. GERHARD RÖNNE, Ugesk. f. læger **103**:1432 (Nov. 6) 1941.

The average vitamin A content of the liver in newborn infants amounts to 25 to 50 international units per gram of liver. From this figure and from the duration in days of the vitamin A–free feeding of newborn and older infants before manifest symptoms of avitaminosis appear, the author calculates that the vitamin A requirement of newborn infants amounts to 20 to 40 international units per kilogram of body weight daily, which corresponds to the requirement of adults. WALLGREN, Göteborg, Sweden.

Newborn

ERYTHROBLASTOSIS FETALIS. RICHARD D. CUTTER and BURT L. DAVIS, California & West. Med. **56**:17 (Jan.) 1942.

Cutter and Davis report a case of congenital hydrops with death within one hour of birth despite an intravenous transfusion. The association of icterus gravis neonatorum, congenital anemia and congenital dropsy is discussed. DAVIS, San Francisco.

A RELIABILITY STUDY OF SPEECH SOUNDS OBSERVED IN THE CRYING OF NEWBORN INFANTS. ORVIS C. IRWIN, Child Development **12**:351 (Dec.) 1941.

In order to determine the degree of observer and of data reliability which can be achieved in the study of speech sounds of infants under 10 days of age, two experiments were conducted. The first included a sample of vowel sounds occurring on 30 respirations of each of 40 infants; the second, a sample for 100 respirations of each of 5 infants. In addition, a further analysis was made of a previously collected body of data. Transcriptions were made in the international phonetic alphabet by two observers working simultaneously and independently. The data under analysis, then, consist of three samples with a total of 3,885 vowel elements.

The following results were obtained: Agreement of observers on crying sounds of the group of 40 infants is 93 per cent with a frequency criterion; with a breath criterion, it is 91 per cent. The range in both cases is from 74 to 100 per cent. With the frequency criterion there was observer agreement above 85 per cent for 36 of the 40 infants. With the breath criterion there was agreement above 85 per cent for 33 of the 40. It is evident that training in transcribing infant sounds on about 18 subjects will yield observer reliability above 90 per cent. There are reasons for believing that when the methods of frequency and breath reliability are both used a more complete result is obtained than when either is used singly. For the separate sounds made by the group of 40 babies, the per cent of observer agreement varied from 60 on

the sound I to 99 on sound H. The average for the five vowels uttered by this group is 85 per cent. A comparison of odd-even items of the vowel sounds of the group of 40 infants shows agreement ranging from 68 to 99 per cent, with an average of 87 per cent. A sample of the sounds of 30 breaths of 40 infants seem to yield more individual sounds than the sample of sounds of 180 breaths of 5 subjects.

It is concluded from these findings that adequate observer and data reliability can be attained in the recording of the speech sounds of newborn infants.

FROM THE AUTHOR'S SUMMARY.

TEMPERATURE AND RADIOSENSITIVITY OF SKIN OF NEW-BORN RATS: IV. EFFECTS OF DECREASED CIRCULATION AND BREATHING DURING IRRADIATION. T. C. EVANS, J. P. GOODRICH and J. C. SLAUGHTER, Radiology **38**: 201 (Feb.) 1942.

A number of experiments were carried on in an effort to overcome the lack of adequate control of the metabolic rate of biologic material in previous reports which have appeared in the clinical and experimental laboratories.

It was found in the first investigation that the radioresistance of the skin of the newborn rats was greatly increased by chilling the animals to 0 C. during the irradiation. A method of measuring the radiation injury was devised, and it was found that for the cold-treated animals the threshold dosage was raised and that above this point the injury increased less rapidly with increased dosage than it did for animals irradiated at room temperature In the third investigation newborn rats were irradiated at temperatures ranging from 0 to 40 C., and it was found that the radiosensitivity increased in proportion to the rise in temperature. The purpose of the present investigation was to determine whether the temperature could have acted through the control of such metabolic processes as rate of blood circulation and breathing. This was done by lowering the metabolic rate by means other than low temperature.

The exposure time in all experiments was fifteen minutes and the dose was 2,010 r. The target distance was 30 cm. The radiation was unfiltered except for 2 mm. of cardboard and the half value layer was about 1.5 mm. of aluminum.

The authors' data indicate that environmental factors during irradiation affect the degree of injury produced in growing mammalian skin. Lowered metabolic rate increased the radioresistance of the skin.

ANSPACH, Chicago.

SHOCK IN THE NEWBORN INFANT. R. A. MILLER, Arch. Dis. Childhood **16**:230 (Dec.) 1941.

The blood chemistry of both mother and infant is disturbed at the time of birth, and hemoconcentration occurs in the infant during the first three to forty-eight hours of life. The biochemical changes may be summarized as follows: There is normally a transient rise in the level of sugar in the blood, which is constantly greater in the mother; the level of nonprotein nitrogen is also elevated in both, but the rise is more pronounced in the infant; the protein and albumin levels are always below the average adult levels, whereas the level of the globulin factor frequently attains the average normal adult value. The deviation from normal is usually more pronounced in the infant than in the mother. Lastly, the sodium and the chloride content of the blood, though frequently within normal limits, are at times exceptionally low. This affects more noticeably the sodium in the mother and the chlorides in the infant.

From the investigations of the blood levels of sugar and of nonprotein nitrogen and the serum levels of globulin and sodium, the following conclusions can be drawn. 1. It may be said that it is better for an infant to have a blood sugar level of less than 11 mg. per hundred cubic centimeters at birth, for in such circumstances its vitality rarely gives cause for anxiety. If hypoglycemia is present, the prognosis is bad (the infant if premature was found to weigh less than 3 pounds [1,307 Gm.] and generally died within an hour of birth; if mature it was stillborn). 2. The concentration of nonprotein nitrogen in the infant's blood varies with the clinical condition, shock being present in 18 per cent of infants with a concentration of less than 40 mg., as compared with almost 50 per cent in infants with a higher concentration. 3. The globulin level of the serum is an even better guide to the clinical condition of the infant at birth (if it fell below 2.06 Gm. per hundred cubic centimeters in the mother or 2.0 Gm. in the infant, there was fetal distress or subnormal vitality at birth in 78 per cent of the cases; but if the concentration of globulin was higher, only 27 per cent of the infants were similarly affected). 4. If the blood contained less than 327 mg. of sodium per hundred cubic centimeters, 43 per cent of the infants suffered from a high degree of shock; but if the content was higher, shock appeared in only 7 per cent of infants.

KELLY, Milwaukee.

NEONATAL THRUSH IN A MATERNITY HOSPITAL. G. B. LUDLAM and J. L. HENDERSON, Lancet **1**:64 (Jan. 17) 1942.

This report comes from the maternity pavilion of the Royal Infirmary, Edinburgh, Scotland. The authors assert that the high incidence and the considerable number of fatalities in the wards of maternity and infants' hospitals are not sufficiently appreciated.

Monilia albicans, the causative yeastlike fungus, infiltrates the buccal mucous membrane with a tangled meshwork of pseudomycelial strands, from which clusters of yeastlike cells known as blastospores are formed by a process of budding.

During 1940 in a group of 2,540 infants who survived more than forty-eight hours 163 were observed to have thrush (6.4 per cent). Although the incidence was somewhat higher in premature infants than in full term, there is no evidence that prematurity predisposes to thrush.

The age of onset of the lesions varied. The earliest appeared on the third day of life. There was a rapid rise of incidence, with the peak occurring on the eighth day.

Oral thrush, though usually without harmful effects in mature infants, often interferes with the appetite of premature babies and may produce serious consequences. Esophageal thrush sometimes develops when the oral lesions have been inconspicuous enough to be missed on routine examination of the mouth.

Of the 163 infants with thrush, 20 died (from various causes) and autopsies were performed on 18. In 8 the thrush had spread to the pharynx, and in 7 of these the esophagus had also been invaded. No intestinal lesions were found. Ebbs (1938) in his series of 22 cases of fatal thrush esophagitis found numerous pinpoint ulcers in the colon in 2.

M. albicans can be isolated by means of mouth swabs several days before the onset of lesions. It can also be isolated from the feces of most infants with oral infection.

Overcrowding in nurseries, breakdown in the rigid nursing routine and use of pooled unboiled breast milk are among the causes of spread in a nursery. Although M. albicans was not uncommonly found in the mother's vagina, there was no significant relationship between vaginal infection and infection in the infant. M. albicans was isolated from the throats of a third of the nurses and from the fingers of a few.

LANGMANN, New York.

THE HEMORRHAGIC SYNDROME IN THE NEWBORN. M. L. AGUIRRE and F. G. ALVAREZ, Arch. argent. de pediat. **13**:26 (Jan.) 1942.

The authors find that the prothrombin time of the mothers in Buenos Aires, regardless of their social conditions, is generally within normal limits similar to those determined for mothers in other cities.

In view of the heterogeneous types of diet taken by the various mothers, the authors come to the conclusion that no definite relation exists between the diet and the prothrombin time. The same applies to the prothrombin time of the mother and the infant; a definite relationship could not be established.

They believe that the decrease in prothrombin in the newborn infant is proportional to the number of hours after birth at which the blood is taken. They believe that the greatest decrease occurs on the second and third days of life. On the fourth day of life there begins a change of the prothrombin time and the usual low level of prothrombin then begins to rise. They believe that this state is physiologic for newborn infants.

SCHLUTZ, Chicago.

Acute Contagious Diseases

CHEMOTHERAPY OF MENINGOCOCCIC MENINGITIS. HAROLD LITTLE, Canad. M. A. J. **45**:509 (Dec.) 1941.

Fourteen cases of meningococcic meningitis are reported, in 10 of which the patients were under 6 years of age. The first 4 patients received serum and sulfapyridine, and the other 10 received sulfapyridine and sodium sulfapyridine alone. The average duration of active symptoms in patients treated with serum was two to three weeks or longer, and not infrequently meningococci were found in the spinal fluid a week or ten days after administration of serum. With chemotherapy the average duration of symptoms was a week or ten days. The clinical picture was completely changed within twenty-four to forty-eight hours after the initial dose.

The dose of sulfapyridine given was 1 grain (0.06 Gm.) per pound (0.5 Kg.) of weight divided into six doses. During the first twenty-four hours this dosage was increased.

One patient in this series died, a child who was moribund when brought to the hospital.

MOORE, Omaha.

STUDIES ON THE HEMOLYTIC STREPTOCOCCUS. A. H. STOCK, L. E. KREJCI, E. B. SANIGAR and E. O. KRAEMER, J. Biol. Chem. **142**:777 and 785 (Feb.) 1942.

The authors report a series of studies dealing with the isolation and purification of a highly concentrated scarlet fever toxin with the aid of improved methods of culture and separation of filtrates.

They were able to obtain from this toxin a heat-coagulable fraction which was alone responsible for the toxic activity and which contained about 200,000,000 skin test doses per milligram.

The authors consider it probable that this heat-coagulable fraction is the actual erythrogenic scarlet fever toxin for the following reasons: 1. They were unable to isolate a heat-coagulable protein from strains of hemolytic streptococci other than the scarlatinal erythrogenic strains. 2. Precipitation experiments showed that toxic activity was associated only with the heat-coagulable protein fraction of the toxin. 3. Electrophoretic purification yielded five constituents, of which only one showed toxic activity, and this was so homogeneous with respect to molecular weight, charge and sedimentation as to provide, in the opinion of the authors, further evidence for its identity with pure erythrogenic scarlet fever toxin.

THOMAS, Chicago.

STUDIES ON CHEMICAL PROPHYLAXIS OF EXPERIMENTAL POLIOMYELITIS. E. W. SCHULTZ and L. P. GEBHARDT, J. Infect. Dis. **70**:7 (Jan.-Feb.) 1942.

There are a number of chemical agents which in aqueous solution of sufficient concentration and efficiently applied to the olfactory mucosa induce in monkeys a well defined resistance against later intranasal instillations of virus. They differ considerably in their power to induce this resistance. Certain ones require repeated application to elicit a clearly defined prophylactic effect, while others provoke a definite and fairly lasting resistance after only one application. An outstanding example of the latter group is a 1 per cent solution of zinc sulfate.

The mechanism underlying the prophylactic effect has in all instances been related to damage to the olfactory mucosa. Substances which are more protective are more damaging than those which are less protective. Zinc sulfate solution, one of the most effective prophylactic agents, induces an extensive coagulation necrosis of the olfactory epithelium, followed usually within a day or two by its separation, more or less en masse, from the lamina propria. The separation is followed promptly by a covering of new epithelium, the cells of which originate from the underlying ducts and glands of Bowman and from the cells of Schwann of nearby olfactory nerve bundles.

The resistant state may not be fully established immediately after a chemical solution is applied. After treatment with zinc sulfate solution part of the animals may continue to prove susceptible to intranasal inoculations for two or three days. During this interim infection continues to take place by the olfactory pathway, as evidenced by inflammatory infiltrations along this pathway and by the fact that previous interruption of the olfactory tract in animals so treated serves to prevent infection.

The resistance induced by a chemical agent is probably never permanent. Animals rendered resistant by applications of zinc sulfate apparently are always resusceptible three to six months after treatment. Demonstrated resusceptibility has always been associated with varying numbers of olfactory nerve cells in the mucosa and with well defined round cell infiltration along the filia of the olfactory nerve and in the olfactory bulb. Various observations suggest that olfactory cells may be regenerated to some extent.

There are reasons for doubting the practical value of chemical prophylaxis for controlling the natural disease in man. These are presented in the body of the paper. Probably the greatest practical use of such a measure is in the prevention of infection by the olfactory pathway in studies designed to elicit other potential portals.

TOOMEY, Cleveland.

PROPHYLACTIC VALUE OF REFINED ANTIPERTUSSIS RABBIT SERUM. WILLIAM L. BRADFORD, HENRY W. SCHERP and ANN M. BROOKS, Proc. Soc. Exper. Biol. & Med. **49**:157 (Feb.) 1942.

Twenty infants exposed to pertussis in the family were given intramuscularly 2 to 10 cc. of concentrated antiserum from rabbits immunized with living Haemophilus pertussis organisms. Thirteen (65 per cent) were completely protected; 5 had mild and 2 had unmitigated attacks. In 3 of the 7 cases the onset was delayed. No general reactions occurred, though 2 of the infants had urticaria at the site of the injection. The expected rate of infection would be about 80 per cent. The effect of the serum seems to be antibacterial rather than antitoxic.

HANSEN, Minneapolis.

SCARLET FEVER IMMUNIZATION: I. AN EVALUATION OF SOME METHODS OF IMMUNIZATION OVER A FIFTEEN YEAR PERIOD. H. C. GRAHAM, South. M. J. **35**:132 (Feb.) 1942.

The author presented some of the various immunization procedures against scarlet fever. He stated that the oral, the inunction and the intradermal method are found to be rather inadequate.

The intranasal method is inadequate unless the immunity is rechecked by the Dick test every one to three years. When a reversal to a positive reaction is found, additional antigenic stimulus must be administered to the point that a negative Dick reaction is obtained or protection is not sufficient.

The Dick subcutaneous injection method confers the most lasting immunity. Whenever reactions occur in its administration, it is quite likely that from this group of reactors will come a higher percentage of reversals to positive than among those with no reactions.

SCHLUTZ, Chicago.

MENTAL SYMPTOMS IN CEREBROSPINAL MENINGITIS. T. W. H. WEIR and C. K. VAUTIER, Brit. M. J. **1**:179 (Feb. 7) 1942.

Weir describes the cases of 3 patients who were admitted to a mental disease hospital with a diagnosis of mental disease. In all 3 of these cases subsequent examinations in the next one to three days revealed definite signs of meningitis. Examination of the spinal fluid revealed evidence of the disease, and meningococci were found both on smear and by culture. It is suggested by the authors that a person in a sudden confused state should not be immediately certified as "insane" but the possibility of his having cerebrospinal meningitis should be considered, particularly since the gathering together of many people, as is necessary in war time, often leads to outbreaks of this disease.

BIRDSONG, University, Va.

DIARRHEA IN THE COURSE OF MEASLES. E. PELUFFO and P. L. ALEPPO, Arch. de pediat. d. Uruguay **13**:31 (Jan.) 1942.

The authors believe that diarrhea is not an essential symptom of measles, such as are, for instance, the respiratory symptoms and others. In the cases in which it was present it coincided with a period when bacillary dysentery was prevalent. The diarrhea did not seem to be a result of the measles infection or a symptom but rather a coincidental infectious complication. The diarrhea of measles seems to coincide with a prevalent bacillary dysentery.

SCHLUTZ, Chicago.

Acute Infectious Diseases

MALARIA RECONNAISANCE OF THE PROVINCE OF PINAR DEL RÍO IN CUBA. HENRY P. CARR and JOAQUIN FERNANDEZ MELENDEZ, Am. J. Trop. Med. **22**:51 (Jan.) 1942.

The authors examined samples of children from every school in the province of Pinar del Río during the period 1938 to 1940. Children of both sexes were examined in approximately the same proportion for splenomegaly. The number of children examined approximated 6 per cent of the total population. Blood smears were taken for approximately 1 per cent of the total population (all children).

They found a significantly higher frequency of children with malaria parasites among those with splenomegaly than in those with normal spleens. Five species of anopheline mosquitoes were encountered: Anopheles albimanus, Anopheles crucians, Anopheles grabhami, Anopheles vestitipennis and Anopheles atropos. Anopheles albimanus was thought to be the most important malaria vector in Pinar del Río Province.

BURPEE, Augusta, Ga.

MALARIA RECONNAISSANCE OF THE PROVINCE OF HAVANA IN CUBA. HENRY P. CARR, JOAQUIN FERNANDEZ MELENDEZ, ALBERTA ROS and ARISTIDES F. MELENDEZ, Am. J. Trop. Med. **22**:63 (Jan.) 1942.

The authors examined children from practically all of the schools except the Habana city metropolitan area during the period 1938 to 1940. In each school a sample number of children were examined for splenomegaly. The total number of children examined in each township constituted about 2 per cent of the total population. Blood specimens from approximately 1 per cent of the population were collected and examined for malaria. All children with palpable spleens were examined for malaria. Both sexes were examined in approximately even proportion. A total of 19,188 children were examined for splenomegaly and 9,982 for malaria parasites.

The authors found the incidence of endemic malaria as a whole low, with the exception of small localized foci which were related to special anopheline problems. The peculiar condition of the soil and subsoil was responsible for the lack of malaria. Four species of anopheline mosquitoes, Anopheles albimanus, Anopheles crucians, Anopheles vestitipennis and Anopheles grabhami, were encountered, but the endemic malaria was caused by Anopheles albimanus.

BURPEE, Augusta, Ga.

DEATH OF AN 11 MONTH INFANT, UNEXPLAINED TO OUR CLINICAL SATISFACTION. Case Rep., Children's Mem. Hosp. **1**:6 (Jan.) 1942.

Clinical and pathologic observations on an 11 month old infant with Salmonella suipestifer sepsis are presented. A blood nonprotein nitrogen level of 102 mg. and a blood sugar level of 370 mg. per hundred cubic centimeters complicated the clinical picture.

DUSHANE. Evanston. Ill.

MILKBORNE OUTBREAK OF BACILLARY DYSENTERY. HEALTH NEWS **18**:188 (Nov. 24) 1941.

One hundred cases of bacillary dysentery, none of which terminated fatally, developed in an up-state school. The disease was traced to bottled milk and bottled chocolate milk. The milk was supposedly pasteurized. It is believed that the milk has been rebottled and recapped.

AIKMAN, Rochester, N. Y.

THE AGGLUTINATION REACTION IN TULAREMIA. JOHN C. RANSMEIER and C. LEROY EWING, J. Infect. Dis. **69**:193 (Nov.-Dec.) 1941.

Ransmeier and Ewing report agglutination titers in 87 nonfatal cases of tularemia, in 10 previously unpublished fatal cases which occurred in Baltimore and in 35 fatal cases collected from the literature.

They compare the development of agglutinins in the blood of patients with fatal and nonfatal forms of the disease and discuss the persistence of agglutinins in the blood for years after recovery from tularemia.

The serums of 24 persons who had handled rabbits in the Baltimore market for long periods were examined, and a high percentage of them were found to contain agglutinins for Bacterium tularense. None agglutinated Brucella abortus. Cross agglutination in tularemia and the undulant fever serums was considered.

The authors found that variation in turbidity of antigen exerted some effect on the end titer of Pact. tularense and B. abortus antiserums.

TOOMEY, Cleveland.

THE BEHAVIOR OF TRYPANOSOMA LEWISI DURING THE EARLY STAGE OF THE INCUBATION PERIOD IN THE RAT. DONALD L. AUGUSTINE, J. Infect. Dis. **69**:208 (Nov.-Dec.) 1941.

Augustine showed that when trypanosomes (Trypanosoma lewisi) are injected into the peritoneal cavity of a rat they are absorbed by the lymphatic system (the lymphatic channels of the diaphragm probably being most significant in the process), pass readily through normal lymph nodes and appear promptly in the thoracic duct and then in the blood stream, in which they remain throughout the infection in this host. Multiplication is not initiated until about two days subsequent to the injection of adult trypanosomes into a noninfected rat, whereas multiplication continues without interruption when forms undergoing rapid division are similarly transferred to a new host. The length of the early incubation period, referred to in the literature as the prepatent period, for T. lewisi is determined by two factors: (1) the number of parasites inoculated and (2) the particular phase of the infection, i. e. age of the parasite, at the time of transfer.

TOOMEY, Cleveland.

PERSISTENCE OF ANTIBODIES ONE YEAR AFTER ACTIVE IMMUNIZATION OF HUMAN BEINGS WITH A MIXED HEAT-KILLED VACCINE OF B. TYPHOSUS,, BR. ABORTUS AND BR. MELITENSIS. JOHN A. KOLMER, AMEDEO BONDI JR., and ANNA M. RULE, J. Infect. Dis. **70**:54 (Jan.-Feb.) 1942.

Agglutination, blood opsonocytophagic and mouse serum protection tests were conducted with the serum of 25 of a group of 29 normal adults one year after the subcutaneous injection of 0.5, 1 and 1 cc. of a heat-killed vaccine carrying 1,000,000,000 each of Bacillus typhosus, Brucella abortus and Brucella melitensis per cubic centimeter, and the results were compared with those observed two weeks after the last dose.

Sixty-eight per cent of the serums showed a reduction in typhoid H agglutinin, but the titers of 100 per cent were above preimmunization levels. One hundred per cent showed a

reduction in typhoid 0 agglutinin, but in 56 per cent the titers were still above preimmunization levels. Ninety-two per cent of the serums showed a reduction of agglutinin for Br. abortus, but 92 per cent showed a persistence of agglutinin above preimmunization levels. Eighty-six per cent of the citrated bloods showed a decrease in phagocytosis for Br. abortus, but the degree of phagocytosis in 90 per cent was above that observed before immunization. Twenty per cent of the serums showed a decrease of mouse-protective antibody for B. typhosus, while 52 per cent showed an increase; 88 per cent of the serums showed the persistence of this antibody above preimmunization levels. Fifty-two per cent of the serums showed a decrease of mouse-protective antibody for Br. abortus, while 36 per cent showed an increase; 88 per cent of the serums showed the presence of this antibody above preimmunization levels. Forty per cent of the serums showed a decrease of mouse-protective antibody for Br. melitensis, while 96 per cent of the serums showed the presence of this antibody above preimmunization levels.

Under the circumstances it appears that antibodies engendered in human beings by heat-killed typhoid-brucella vaccine persist satisfactorily for at least one year and that the mixed vaccine may be worthy of clinical trial for simultaneous vaccination against typhoid and undulant fevers.

TOOMEY, Cleveland.

SULFANILYLGUANIDINE AND SULFANILAMIDE IN THE TREATMENT OF LYMPHOGRANULOMA VENEREUM INFECTIONS OF MICE. ENID C. RODANICHE, J. Infect. Dis. **70**:58 (Jan.-Feb.) 1942.

Both sulfanilamide and sulfanilylguanidine were found to be effective therapeutic agents against meningoencephalitis of mice induced by injections of lymphogranuloma virus. In the concentrations used, sulfanilylguanidine was more effective and less toxic than sulfanilamide.

Administration of these drugs in no way interfered with the development of an active immunity in mice.

No sterilization of the brain was effected by either compound.

TOOMEY, Cleveland.

SULFAGUANIDINE IN THE TREATMENT OF BACILLARY DYSENTERY. L. B. EDWARDS, South. M. J. **35**:48 (Jan.) 1942.

The author states that in using sulfaguanidine in the treatment of bacillary dysentery it must be remembered that its action is antibacterial. Its administration must be supplemented with proper measures necessary to prevent and combat the dehydration, acidosis and other complications that may occur in the course of the disease. The drug should be used as early after onset of symptoms as possible.

The dosage suggested for children is 0.05 Gm. per kilogram of body weight given every four hours when diarrhea is present until the stools decrease to five or less daily; then 0.1 Gm. per kilogram should be given every eight hours for at least three days. It should rarely, if ever, be given for more than fourteen days. During administration of the drug, emphasis should be laid on proper fluid intake and the maintenance of a good urinary output.

Administration of vitamins is important, particularly if the patient gives evidence of a previous insufficient diet or if the course of the disease is prolonged and proper assimilation of the vitamins in the diet is therefore necessarily impaired.

SCHLUTZ, Chicago.

TREATMENT OF ACUTE BACILLARY DYSENTERY WITH SULFANILYLGUANIDINE. A. J. QUICK, Wisconsin M. J. **40**:1064 (Nov.) 1941.

Acute bacillary dysentery is a serious infectious disease especially in children. Previously used drugs (bismuth, phenyl salicylate, etc.) have limited value. Sulfanilylguanidine, acting effectively against the pathogenic organism and being poorly absorbed, has great value in this infection. It is given in doses of 0.1 Gm. per kilogram of body weight internally and then 0.05 Gm. per kilogram every four hours until the stools are reduced to five or less per twenty-four hours. Thereafter, this amount is given every eight hours. The administration of the drug can usually be stopped in two or three days. The drug may be given as a fine powder suspended in milk and rarely causes trouble. Other supportive treatment is given as indicated.

JANNEY, Wauwatosa, Wis.

INFLUENZA VIRUS "A" INFECTIONS OF CYNOMOLGUS MONKEYS. F. M. BURNET, Australian J. Exper. Biol. & M. Sc. **19**:281 (Dec.) 1941.

Burnet reports that cynomolgus monkeys (Macacus irus) are susceptible to infections with strains of influenza virus when material of high titer is administered intratracheally. The infection involves predominantly the epithelium of the smaller bronchioles. Limited experiments on

immunization indicated that (*a*) recovery from a preceding intratracheal infection with virus gave a solid immunity against symptomatic reinfection, (*b*) subcutaneous inoculation of living virus gave effective immunity, (*c*) subcutaneous inoculation of formaldehyde-treated virus was not effective, (*d*) intranasal instillation of active virus was also ineffective and (*e*) the degree of immunity was correlated with the antibody level. GONCE JR., Madison, Wis.

TYPHOID CARRIERS AND THEIR TREATMENT. T. M. VOGELSANG, Nord. med. (Med. Rev.) **12**:3065 (Nov. 1) 1941.

Vogelsang reports on 23 carriers of typhus or paratyphoid B, of whom 1 was a child, a boy of 9 years. After his acute illness he continued to excrete typhoid bacilli in the stools. There was clinical and roentgenologic evidence of involvement of the gallbladder. Six months after the onset of the disease cholecystectomy was performed. There was no concrement, but distinct histologic signs of chronic cholecystitis were found. Typhoid bacilli could be demonstrated in the wound up to eleven days after the operation and in the stools up to one month. The bacteriologic tests then gave negative results. The boy was considered cured.

WALLGREN, Göteborg, Sweden.

UNDULANT FEVER IN AN INFANT. BERTIL SÖDERLING, Svenska läk.-tidning. **38**:2880 (Dec. 24) 1941.

A 13 month old boy fell ill with fever. He was first seen one week later. At that time his temperature was 38.3 C. (100.9 F.). There were no catarrhal symptoms. The patient reacted negatively to tuberculin. A serologic test elicited a positive response for undulant fever. He was free of symptoms three days later. The infant had been fed raw milk from cows which were shown to be suffering from Bang's disease.

WALLGREN, Göteborg, Sweden.

INFECTIOUS MONONUCLEOSIS. TORSTEN THYSELL, Svenska läk.-tidning. **38**:2887 (Dec. 24) 1941.

Thysell reports on an infectious disease in a 3 year old boy who fell ill with fever. There were pronounced edema of the eyelids, a macular exanthem, enlargement of the liver and spleen and slight swelling of the lymphatic glands of the neck but no tonsillitis. The white blood cell count was 19,600, with 90 per cent lymphocytes, monocytes and large abnormal mononuclear cells. The Paul-Bunnel test produced a negative reaction. The patient was discharged healthy and free of clinical symptoms two months later.

WALLGREN, Göteborg, Sweden.

TREATMENT OF PNEUMONIA IN CHILDREN WITH A SINGLE LARGE DOSE OF SULFATHIAZOL. C. FRIDERICHSEN and P. SÖBYE, Ugesk. f. læger **103**:1331 (Oct. 16) 1941.

The authors report on treatment with one large dose of sulfathiazole in 70 cases of acute pneumonia in children as compared with treatment with repeated smaller doses during four days in 59 cases. They emphasize that the single massive dose treatment simplifies the therapy, is somewhat less expensive and gives the same therapeutic effect as the treatment with repeated smaller doses.

WALLGREN, Göteborg, Sweden.

PURULENT MENINGITIS TREATED WITH SULFONAMIDE COMPOUNDS. H. C. ENGDAEK, N. I. NISSEN and A. H. SCHLESNER, Ugesk. f. læger **103**:1599 (Dec. 11) 1941.

By the treatment of purulent meningitis with sulfonamide compounds the death rate of meningococcic and streptococcic meningitis has been lowered to 20 per cent, of Pfeiffer bacillus meningitis to 50 per cent and of pneumococcic meningitis to 75 per cent. It is important to begin the treatment with large doses. A maximum concentration of the drug in the serum is attained more quickly with sulfapyridine than with sulfathiazole or sulfamethylthiazole.

WALLGREN. Göteborg, Sweden.

Chronic Infectious Diseases

A SURVEY OF PERSONS EXPOSED TO TUBERCULOSIS IN THE HOUSEHOLD. HENRY BEEUWEKES, RICHARD G. HAHN and PERSIS PUTMAN, Am. Rev. Tuberc. **45**:165 (Feb.) 1942.

The 502 families studied in this survey included 2,221 persons. Positive reactions to tuberculin and tuberculous lesions were encountered more frequently among persons exposed to tuberculosis in patients with tubercle bacilli in the sputum than among those exposed to tuber-

culosis in patients with no known tubercle bacilli in the sputum. This was particularly true of infants and young children. The lesions among those exposed to open tuberculosis were likewise of a more serious type.

This study brought out the importance of a prolonged period of observation of contacts if asymptomatic and manifest disease are to be detected in their incipiency. Over one-half of the infants and young children who were exposed in infancy and later acquired clinical tuberculosis did so over a period of twenty years. On the other hand, persons who were from 15 to 25 years old at the time of initial exposure manifested clinical tuberculosis after a much shorter interval.

The frequency with which persons in contact with tuberculosis should be examined varies with age. Children between the ages of 5 and 10 years do not need as frequent examinations as those under 5 years. During adolescence and young adulthood, examinations should be made more frequently. Also persons in contact with persons having bacilli in the sputum should be watched more carefully.

The significance of asymptomatic infiltrating lesions was emphasized by the observation that of 87 contacts found with such lesions at their initial examination 11 progressed to manifest disease.

Of 1,674 persons exposed to the disease, 139 acquired manifest disease at various intervals during a period of twenty-five years following the initial exposure.

EUGENE SMITH, Ogden, Utah.

TUBERCULIN PATCH TEST: ITS RELIABILITY. PETER COHEN, California & West. Med. **56**:70 (Feb.) 1942.

The Vollmer-Lederle patch test was applied to 1,535 persons, mostly school children, simultaneously with the Mantoux test, purified protein derivative being used. The results of the two tests were the same for 1,520 subjects (99 per cent of those tested). The patch test gave a positive reaction in 11 subjects who did not react to the Mantoux test, while the Mantoux test elicited a positive reaction in 4 whose reactions to the patch test were negative.

DAVIS, San Francisco.

TUBERCULIN TESTS IN CHILDREN. CLEMENT A. SMITH, WILLIAM H. FAULKNER and JOSEPH M. CORDI, New England J. Med. **225**:1008 (Dec. 25) 1941.

It has been the usual custom to perform the intradermal, or Mantoux, tuberculin test in the outpatient department of the Boston Children's Hospital by injecting 0.1 cc. of old tuberculin diluted 1:1,000. As a result of this dilution, an actual dose of 0.1 mg. of tuberculin comes in contact with the intracutaneous tissues.

In this study, when a child in the hospital was discovered to react to the routine test with 0.1 mg. of tuberculin and was not deemed an unfavorable subject because of fever, serious illness or other cause, he was retested on the other arm with simultaneous injections of 0.1, 0.01 and 0.001 mg. of tuberculin, respectively, or 0.1 cc. of 1:1,000, 1:10,000 and 1:100,000 dilutions. The preparation used consists of old tuberculin supplied by the Saranac Laboratories and made up to the proper strength with phenolized solution of sodium chloride. Fresh dilutions are made once a month and kept in refrigerators when not in use.

This experimental procedure was also used to test 75 children in various stages of tuberculous disease and healing at the North Reading State Sanatorium. This study gave an excellent opportunity to compare the sensitivity of the Vollmer tuberculin patch test with the response of children to various strengths of old tuberculin administered by the Mantoux technic. The results of all the tests are discussed and tabulated.

True and false positive reactions are also discussed.

Simultaneous intradermal (Mantoux) tests with graded doses of old tuberculin were performed on 336 infants and children under 13 years of age. The same patients were tested by the patch method.

Test doses of less than 0.1 mg. were less than 85 per cent as accurate as doses of 0.1 mg. in revealing sensitivity to tuberculin. Doses of 0.1 mg. were 97 per cent as accurate as those above that amount.

The tuberculin patch test elicited positive reactions in 113 (97 per cent) of 116 children who reacted to 0.1 mg. or less of old tuberculin by the intradermal method.

No correlation between sensitivity to tuberculin and degree of infection was apparent.

GENGENBACH, Denver.

QUANTITATIVE STUDIES OF THE TUBERCULIN REACTION: II. THE EFFICIENCY OF A QUANTITATIVE PATCH TEST IN DETECTING REACTORS TO LOW DOSES OF TUBERCULIN. MICHAEL L. FURCOLOW, Pub. Health Rep. **56**:2405 (Dec. 19) 1941.

On a group of 612 children on whom a patch test was performed and who had also had an intracutaneous injection of 0.0001 mg. of the purified protein derivative the following observations were made: The more sensitive the person the greater the reaction to the patch test. The most potent patch (1 per cent of purified protein derivative) will detect most reactors. If it is accepted that reactors to 0.0001 mg. or less of purified protein derivative include almost all persons whom it is desirable to detect, the patch test will detect such persons with an error of 6 per cent missed and 7 per cent extra reactors.

SANFORD, Chicago.

OBSERVATIONS ON THE MASSIVE DOSE ARSENOTHERAPY OF EARLY SYPHILIS BY THE INTRAVENOUS DRIP METHOD: III. PREGNANCY, AND ITS OUTCOME, ASSOCIATED WITH OR FOLLOWING THE TREATMENT OF EARLY SYPHILIS BY MASSIVE ARSENOTHERAPY. JOSEPH F. SADUSK JR. and THOMAS E. SHAFFER, Yale J. Biol. & Med. **14**:365, 1942.

1. The case histories are described of 2 women who had received massive dose arsenotherapy for early syphilis shortly before the onset of pregnancy. Each patient was delivered of a normal, full term infant. Neither child showed clinical, serologic or roentgenologic evidence of congenital syphilis during a six month follow-up period.

2. The treatment by means of massive dose arsenotherapy of 2 additional pregnant patients with secondary syphilis is described. The course of therapy in each instance was uneventful. Neither patient had delivered at the time of the report; consequently no data are available concerning the fetus.

AUTHORS' SUMMARY.

GASTRIC LAVAGE IN THE DIAGNOSIS OF TUBERCULOSIS IN CHILDREN: A SURVEY OF 75 CASES. T. W. DAVIES and C. J. DOHERTY, Brit. M. J. **1**:212 (Feb. 14) 1942.

Seventy-five children with tuberculosis were investigated in the survey reported. Sixty-four of these had pulmonary tuberculosis or a pulmonary lesion, and eleven had a nonpulmonary form of the disease. Gastric lavage was done by means of a no. 10 rubber catheter, and the stomach was washed out with from 200 to 300 cc. of sterile water. In the stomach contents of 24 (37 per cent) of the 64 children with pulmonary tuberculosis tubercle bacilli were found on direct examination after concentration or in culture or in guinea pig inoculation. Tubercle bacilli were not obtained from the gastric contents of subjects with nonpulmonary tuberculosis. It is stated that because it is sometimes difficult to make a diagnosis of tuberculosis for a patient with a positive reaction to a tuberculin test and with a pulmonary lesion the recovery of the tubercle bacillus by gastric lavage is helpful. It was also stated that since these children have actual tubercle bacilli present in their excretion they should be regarded as dangerous and should be segregated.

In the summary the authors state the belief that gastric lavage should be a routine diagnostic measure and that the procedure should be done on successive days and frequently during treatment of the disease.

BIRDSONG, University, Va.

STUDIES IN TUBERCULOSIS: V. BIOPSY STUDY OF LYMPHATIC GLAND IN THE DIAGNOSIS OF TUBERCULOUS DISEASE OF JOINTS. R. WEBSTER, M. J. Australia **1**:160 (Feb. 7) 1942.

Even though clinically imperceptible, tuberculous lymphadenitis was demonstrated by histologic and cultural observations on the inguinal lymph nodes of 6 of 7 patients, all but 1 of whom were children, suffering from tuberculosis of the knee joint; in glands of the same group (inguinal) in 2 of 6 children suspected of having tuberculosis of the hip joint; in an inguinal gland also of 1 adult patient exhibiting advanced tuberculosis of the ankle joint, and in an axillary gland of a child affected with tuberculosis of the wrist joint. Confirmation of a provisional diagnosis of early tuberculosis of the knee and perhaps other joints can be attained by such study. However, the finding of tuberculosis in lymphatic glands of the inguinal group should not be accepted as significant of tuberculous disease of the hip joint, because of the anatomic arrangement of the lymphatic structures of this joint and because of the impossibility of exclusion of metastasis from apparently insignificant and healed cutaneous lesions.

GONCE JR., Madison, Wis.

TUBERCULOUS MENINGITIS OF BOVINE ORIGIN. C. J. DU TOIT and G. BUCHANAN, South African M. J. **16**:10 (Jan. 10) 1942.

The author reports a single case of tuberculous meningitis of bovine origin. Although the occurrence of infection with the bovine type of tubercle bacillus in childhood has long been

suspected because of the particular sites of infection in children and the common occurrence of tuberculosis in South African cattle, human infection with the bovine tubercle bacillus has been recorded in South Africa in only 1 other instance. GONCE JR., Madison, Wis.

THE TUBERCULIN PATCH TEST. MIGUEL F. PASTOR and ROBERT J. d'EMPAIRE, Rev. méd. latino-am. **27**:396 (Jan.) 1942.

Of 88 persons known to be infected with tuberculosis the reactions to the patch test of Vollmer were positive in 85.22 per cent. When the reaction to a patch test is negative, an intradermal test with a 1:10 dilution of old tuberculin should be done.

DWYER, Kansas City, Mo.

BONE SYPHILIS IN INFANCY. JOÃO F. FORTES, Rev. méd. munic. **3**:7 (Jan.) 1942.

Sixty-four illustrative roentgenograms are shown of syphilitic osteochondritis, osteoperiostitis and osteomyelitis. These are interesting, as are also other demonstrations of differentiation between scurvy, rickets and syphilis. SANFORD, Chicago.

Diseases of Blood, Heart and Blood Vessels and Spleen

VISUALIZATION AND OBLITERATION OF ANGIOMATA BY RADIOPAQUE SOLUTIONS. MAURICE M. POMERANZ and ISIDORE S. TUNICK, Ann. Surg. **114**:1050 (Dec.) 1941.

The authors review 256 cases of muscular angiomas reported in the literature up to 1932 and add 4 cases of their own. The fact that 47 per cent of the growths occurred during the first decade of life suggests that the condition is congenital. That trauma may be of significance is evidenced by the fact that 17 per cent of the tumors followed injury.

There is often a history of slowly developing tumor, which is noted at birth or shortly thereafter. Pain is usually a prominent feature. It may be present at the site of the tumor or radiate down the extremity. The tumor varies in size from a small nodule to a mass the size of a small orange.

The roentgenographic demonstration of phleboliths in the muscles of an extremity is evidence of this disease, but the tumors may exist without the presence of phleboliths. The most accurate aid to diagnosis is the injection of a radiopaque substance in order to visualize and identify the lesion. After the diagnosis is made, the injection of obliterating mediums may give satisfactory relief and avert open operation. Injections need not be made into small angiomas in children, since they may spontaneously retrogress without treatment.

BANTIN, Omaha.

THE BRAIN IN SICKLE CELL ANEMIA. FREDERIC WERTHAM, NATHAN MITCHELL and ALFRED ANGRIST, Arch. Neurol. & Psychiat. **47**:752 (May) 1942.

The essential neuropathologic features of sickle cell anemia are small, necrotic and necrobiotic lesions on a vascular basis, which are diffusely distributed, with predilection for the border between the cortex and the subcortical white matter; pronounced general hyperemia and congestion of blood vessels; hypertrophy and proliferation of endothelial and adventitial elements of the walls of small blood vessels; siderotic pigment in intra-adventitial spaces and adventitial cells; larger vascular lesions of uncharacteristic type (softenings and thromboses); small hemorrhages and extravasations; intravascular deposits of lipoid material and fat embolism of capillaries and precapillaries; focal and diffuse changes in the nerve cells in cortical and subcortical gray structures, and focal areas of demyelination in the spinal cord similar to those seen in subacute combined degeneration. BEVERLY, Chicago.

CONGENITAL HEMOLYTIC ANEMIAS. HENRY L. SCHMITZ and GEORGE J. ANDAY, M. Clin. North America **26**:219 (Jan.) 1942.

Congenital hemolytic anemias (familial hemolytic icterus, Cooley's erythroblastic anemia and sickle cell anemia) have the following features in common: an insidious onset usually dating back to earliest childhood, jaundice, splenomegaly and anemia. Pain in the upper part of the abdomen, dull or fleeting, or in the form of an "abdominal crisis," is of frequent occurrence. Ulcers on the legs are common in sickle cell anemia and in Cooley's anemia and may occur in congenital hemolytic jaundice. All three are characterized by fluctuations in the severity of symptoms. Roentgen changes in the skull and long bones occur, particularly in erythroblastic anemia and sickle cell anemia. Changes in the blood consist of varying degrees of anemia with a high reticulocyte count and a normal—but usually elevated—white cell count. The morphology and the fragility of the erythrocytes vary in the different types, and it is on the basis of these that the differentiation is made.

Familial hemolytic icterus is hereditary. The blood picture is characterized by spherocytosis. Spherocytes are spherical erythrocytes which appear smaller and thicker than normal and lack the usual central area of pallor. The fragility of the red cells is usually increased. Excellent results are obtained in congenital hemolytic jaundice by splenectomy.

Cooley's anemia is congenital but apparently not hereditary, and is peculiar to the Mediterranean races. The blood changes are characteristic: pronounced anisopoikilocytosis and erythroblastosis. In most instances the fragility test shows increased resistance. The mongoloid facies is typical in the more severe forms of this disease. Treatment is symptomatic; splenectomy is usually of no benefit.

Sickle cell anemia occurs frequently in the Negro race. A typical specimen of blood from a patient with the disease shows marked anisopoiklocytosis and the presence of sickle cells. The fragility of the red cells is usually near normal. Treatment is unsatisfactory. Splenectomy may give some benefit if done early in the disease, when the spleen is still large.

EUGENE SMITH, Ogden, Utah.

EFFECT OF CONGO RED ON PLASMA PROTHROMBIN. W. A. BARNES, Proc. Soc. Exper. Biol. & Med. **49**:15 (Jan.) 1942.

When the plasma prothrombin in mice was reduced by the administration of liquid petrolatum, 0.1 cc. of a 1 per cent solution of congo red injected intraperitoneally for three to eight days caused an average increase of 23 per cent in the prothrombin level. Similar effect of congo red was noted on 2 dogs which had low prothrombin levels following cholecystectomy. The authors believe that the hemostatic effect of congo red in some cases may be explained, at least in part, by its vitamin-K-like action in raising the plasma prothrombin level.

HANSEN, Minneapolis.

EFFECT ON COAGULATION TIME OF ORAL ADMINISTRATION OF RABBIT THROMBIN. HENRY J. TAGNON and F. H. L. TAYLOR, Proc. Soc. Exper. Biol. & Med. **49**:32 (Jan.) 1942.

Rabbit thrombin (preparation of pseudoglobulin of rabbit plasma having high clot-promoting activity) described by Parfentjev (*Am. J. M. Sc.* **202**:578, 1941). administered to dogs and normal human subjects caused a decrease in the coagulation time. For the human subjects 10 Gm. of the material was dissolved in tomato juice. For 2 patients with hemophilia the coagulation time promptly dropped to a minimum in one hour and began to return by two hours.

HANSEN, Minneapolis.

FACILITIES FOR CARE OF CHILDREN WITH RHEUMATIC HEART DISEASE. O. F. HEDLEY, Pub. Health Rep. **56**:2321 (Dec. 5) 1941.

This is an excellent summary of the present institutions that care for children with heart disease and should be read in detail by persons interested. It contains a description of special institutions, hospitals for patients with rheumatic heart disease, sanatoriums for children convalescent from cardiac disease, general convalescent institutions furnishing care to children with rheumatic heart disease and foster homes. There is also a discussion of the type of care, facilities and personnel necessary for the proper care of such children.

SANFORD, Chicago.

THROMBOSIS OF THE SPLENIC VEIN. D. FUKS, Arch. argent. de pediat. **13**:61 (Jan.) 1942.

The author reports a case of thrombosis of the splenic vein in a child aged 6 years. The condition manifested itself by severe hematemesis, epigastric pain and splenic enlargement. Severe anemia developed in the course of the disease.

A splenectomy was performed. The spleen on section showed marked reticulofibrosis and follicular hypoplasia. There were no sclerotic changes such as are seen in Banti's disease.

The child recovered well from the operation but on the fifth day died suddenly from a condition which the surgeon called surgical tetany.

SCHLUTZ, Chicago.

Diseases of Nose, Throat and Ear

FINAL REPORT ON MILKBORNE SEPTIC SORE THROAT OUTBREAK IN SUFFOLK COUNTY. Health News **19**:23 (Feb. 9) 1942.

This epidemic was traced to raw milk which had been infected by a milk handler who was suffering from sore throat. Strains of hemolytic streptococci belonging to Lancefield serologic group A, which is the group usually associated with human infections, were

isolated by the state laboratory from the milk of the infected cow, from cultures of material from the throat of the milk handler and from a number of patients.

AIKMAN, Rochester, N. Y.

THE RESULTS OF TREATMENT WITH BACILLUS COLI METABOLIN IN ALLERGIC RHINITIS. HARRY H. SHILKRET, New York State J. Med. **42**:332 (Feb. 15) 1942.

Shilkret makes an exhaustive analysis of the work of Elsbach, concerned with a "cure" for hay fever (*N. Y. State J. Med.* **41**:1248 [June 15] 1941). In that article Elsbach reported 75 cases of "desensitization" of the nasal mucous membrane with a preparation containing the products of metabolism of Bacillus coli found in the human intestine (B. coli metabolin). Newspapers played up the "discovery," and many physicians throughout the United States asked for supplies of the agent so that they might try it on their patients. In the City Hospital and in the French Hospital, Shilkret studied 20 cases intensively. He tabulates his protocols and his results. In order that no other investigator may travel over the same road and follow an *ignis fatuus*, Shilkret concludes: "B coli metabolin is of no value in the treatment of hay fever or allergic coryzas." VOORHEES, New York. [ARCH. OTOLARYNG.]

Diseases of Lungs, Pleura and Mediastinum

ACUTE EFFECTS OF SMOKING ON RESPIRATION AND CIRCULATION. ROLLAND J. MAIN, Proc. Soc. Exper. Biol. & Med. **48**:495 (Nov.) 1941.

Six male subjects in their early twenties were found to have a decrease in the alveolar carbon dioxide tension and a rise in the blood pressure and heart rate when smoking a regular cigaret (2 per cent nicotine) one puff every half-minute with deep inhaling. The alveolar carbon dioxide tension decreased for from ten to thirty minutes while the increased blood pressure and rapid pulse rate persisted for from thirty to sixty minutes. When they smoked nicotine-free cigarets, much less effect was produced. HANSEN, Minneapolis.

TREATMENT OF BRONCHOPNEUMONIA IN CHILDREN UNDER ONE YEAR OF AGE. Rev. mex. de pediat. **11**:481 (Dec.) 1941.

Bronchopneumonia in children under 1 year of age is considered a grave disease, according to figures of English authors. In the series reported, cases were observed during the winter of 1939-1940.

The usual history starts with an infection of the upper respiratory tract. The fatal cases of bronchopneumonia are those with intense cyanosis, those with complicating convulsions and those in which the patient is in poor condition. In this series the mortality rate, relatively reduced, was 36 per cent, owing principally to the administration of sulfapyridine and to the use of oxygen.

The usual dose of sulfapyridine was 0.125 Gm. up to 3 months of age and 0.25 Gm. from 3 months to 1 year, every four hours. The initial dose was double the usual dose. Oxygen was given in the usual way.

Other therapeutic measures were also used: liberal administration of liquids and food every two hours night and day, induction of sleep by use of chloral hydrate and proper care.

GIFFEN, Toledo, Ohio.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

THE OCCURRENCE OF AVITAMINOSIS A IN DISEASES OF THE LIVER. MICHAEL G. WOHL and J. B. FELDMAN, Am. J. Digest. Dis. **8**:464 (Dec.) 1941.

Thirty-six patients with various forms of hepatic disease were investigated. An ophthalmologic examination was made to exclude the possibility of pathologic conditions of the retina or choroid having anything to do with the dark adaptation test for vitamin A deficiency.

Their results show (1) that when jaundice is the result of severe hepatic damage, the dark adaptation test is abnormal; (2) that when severe hepatic damage occurs without jaundice, the dark adaptation test also is abnormal, and (3) that when jaundice occurs without extensive damage to the liver, dark adaptation approximates the normal.

The usual laboratory and clinical estimations of hepatic function may be augmented by the routine use of the dark adaptation test with certain qualifying points, such as absence of intrinsic retinal disease, pathologic conditions of the gastrointestinal tract interfering with absorption and adequate intake of vitamin A among others. MORRISON, Savannah, Ga.

DISTANT NEUROANATOMIC COMPLICATIONS OF SPINA BIFIDA (SPINAL DYSRAPHISM): HYDROCEPHALUS, ARNOLD-CHIARI DEFORMITY, STENOSIS OF THE AQUEDUCT OF SYLVIUS, ETC.; PATHOGENESIS AND PATHOLOGY. BEN W. LICHTENSTEIN, Arch. Neurol. & Psychiat. **47**:195 (Feb.) 1942.

In some cases of spina bifida, during development there is a fixation of the spinal cord at the level of the sacrum, so that it can not move upward in the spinal canal normally as growth takes place. As a result, the hindbrain is pulled into the spinal canal, with localization in the canal of the medulla oblongata, choroid plexus of the fourth ventricle and parts of the cerebellum. There may also result a stenosis of the aqueduct of Sylvius causing internal hydrocephalus, syringomyelic-like cavitation in the cervical portion of the canal and pressure on the anterior spinal arteries and the vertebral system of veins at the foramen magnum. These conditions are known as Arnold-Chiari deformity. BEVERLY, Chicago.

PYRUVIC ACID STUDIES IN THE WERNICKE SYNDROME. HERMAN WORTIS, ERNEST BUEDING, MARTIN H. STEIN and NORMAN JOLLIFFE, Arch. Neurol. & Psychiat. **47**:215 (Feb.) 1942.

Wernicke's syndrome is characterized by clouding of consciousness, varying ophthalmoplegias and ataxia. Pathologically, the lesions are confined to the periventricular gray matter and are characterized by small foci of degeneration and varicose deformities of the blood vessels. In studying 11 patients, the authors found the fasting level of pyruvate in the blood invariably elevated, an indication of inability of these patients to metabolize pyruvic acid properly. They state:

"After prolonged treatment with thiamine hydrochloride and with thiamine hydrochloride plus other members of the vitamin B complex, this defect in pyruvic acid metabolism is corrected. This is associated with disappearance of the ophthalmoplegia and improvement in the mental status.

"Our clinical and chemical observations, together with the pathologic changes previously reported by Alexander and his co-workers, demonstrate that the Wernicke syndrome is invariably associated with a deficiency of thiamine." BEVERLY, Chicago.

ENCEPHALITIS WITH INTRANUCLEAR INCLUSION BODIES: A CLINICOPATHOLOGIC STUDY. ANDREW J. AKELAITIS and LOUIS J. ZELDIS, Arch. Neurol. & Psychiat. **47**:353 (March) 1942.

The authors report a case of acute encephalitis with an unusual clinical and pathologic picture. There was an acute onset with crying and stiffness and twitching of the left arm, which extended five days later to the left leg. These attacks were paroxysmal and were best described as acute torsion spasms of the left arm and leg with arching of the neck and flexion of the body to the left. Between attacks the arm and leg remained stiff. There was no Babinski response on either side and no clouding of consciousness. There was some fever, a spinal fluid cell count of 3 to 5 and a high sugar level. There was some involvement of the right side twelve days after onset. The course was downhill, with eventual coma and death nine weeks after the onset.

Pathologically, this was found to be a necrotic form of encephalitis with intranuclear inclusion bodies. This is unlike the picture of virus encephalitis. BEVERLY, Chicago.

SPINA BIFIDA WITH MENINGOCELE: OCCURRENCE IN TWO CHILDREN OF THE SAME FAMILY. BERNARD HAROLD SHULMAN, Arch. Neurol. & Psychiat. **47**:474 (March) 1942.

The author reports the occurrence of spina bifida with meningocele in 2 children in the same family. BEVERLY, Chicago.

MARKED ABDOMINAL DISTENTION SOON AFTER BIRTH. Case Rep., Children's Mem. Hosp. **1**:7 (Feb.) 1942.

A newborn infant with pronounced abdominal distention was found to have a ruptured cecum at operation. An additional finding at autopsy was fibrocystic disease of the pancreas. DUSHANE, Evanston, Ill.

ASSOCIATION OF LUNG AND PANCREATIC DISEASE. Case Rep., Children's Mem. Hosp. **1**:10 (Feb.) 1942.

Atypical clinical observations on a 10 week old boy with multiple pulmonary abscesses and fibrocystic disease of the pancreas are discussed. DUSHANE, Evanston, Ill.

UNUSUAL EXPERIENCES WITH APPENDICITIS. Case Rep., Children's Mem. Hosp. **1**:13 (Feb.) 1942.

Dr. A. H. Montgomery discussed 6 unusual cases of appendicitis in children, stressing methods of diagnosis and treatment. The youngest patient was 27 months old.

DUSHANE, Evanston, Ill.

SPASTIC COLITIS IN INFANCY AND CHILDHOOD. CHARLES JAMES BLOOM, New Orleans M. & S. J. **94**:322 (Jan.) 1942.

As a pediatric entity spastic colitis was first described in 1931, classified into four types: (1) essential spastic colitis, due to faulty intestinal mechanics influenced by lack of autonomic regulation (no demonstrable lesion or anomaly); (2) spastic colitis due to a pathologic condition of the abdomen within or outside the intestinal tract; (3) spastic colitis due to an anomaly of the intestinal tract, and (4) spastic colitis due to purgatives, alcohol, poisons or spoiled food or a residual of bacillary dysentery and amebiasis.

A series of 66 cases is reported, in 30 of which the colitis was classified as of type 1, in 26 as of type 2 and in 10 as of type 3.

Gentiles are more often involved than Jews; males predominate 1.5 to 1 over females, and in 40 of the 66 cases the condition occurred between the ages of 6 and 15 years.

In order of frequency the outstanding symptoms are anorexia, nausea and vomiting, abdominal pain, undernutrition, constipation and restlessness at night. Treatment by psychologic means, diet and drugs is discussed.

BERKLEY, Beverly Hills, Calif.

INFANTILE DIARRHOEA AND VOMITING. R. M. CAMPBELL and A. A. CUNNINGHAM, Arch. Dis. Childhood **16**:211 (Dec.) 1941.

In a series of 574 cases of gastroenteritis in infants under 2 years of age there was a death rate of 27.7 per cent.

While the general nursing management must be of a high order to insure success with consistently good results, the most important single factor is the relief of dehydration. Constant subcutaneous infusions, supplemented in cases of severe gastroenteritis by fluid given either by the intraperitoneal or by the intravenous route, are valuable. The death rates in 283 cases of gastroenteritis with dehydration (53 per cent) is in sharp contrast to that in 291 cases without dehydration (2.4 per cent) and serves to emphasize the great importance of a careful assessment of the water balance in infants with this malady.

The continuous injection of fluids subcutaneously is favored in the treatment of dehydrated infants. Physiologic solution of sodium chloride, Ringer's solution and 3 per cent dextrose in a 0.25 per cent solution of sodium chloride were the fluids given.

The use of whole blood was found to be of value only for patients with definite anemia or with a long-standing infection, such as otitis media. Transfusions of plasma as recommended by Aldridge (1938) are valuable in the later stages of illness when there is hypoproteinemia, whether with or without edema. When the protein of the serum is maintained at a normal level, therapy by the continuous subcutaneous injection of fluids can be employed. Blood transfusions are therefore chiefly of value for rather older infants, approximately 9 months of age or older, as they appear to tide the child over the danger period till he reaches an age when the recuperative powers of the body are better developed.

KELLY, Milwaukee.

ESOPHAGITIS OF INFANTS. D. REYE, M. J. Australia **2**:673 (Dec. 13) 1941.

Among 150 consecutive autopsies at a children's hospital 10 cases of esophagitis were discovered. In 3 of these the condition occurred as a complication of some other fatal disease, but in 7 cases the esophagitis was the primary cause of death. The direct etiologic factors were thrush (5 cases), undetermined (1 case) and hemolytic streptococci of group B (1 case). The age incidence was 2 weeks to 11 months. The outstanding symptom in all cases was vomiting, which occurred during or soon after feeding. At some time or throughout the duration of the illness the vomitus was discolored a dark brown by altered blood. The esophageal lesion usually appeared as a gray to brown surface exudate limited to the distal third of the esophagus. In all cases the stomach contained large amounts of black material, which proved to be mucus mixed with altered blood. The author believes that esophagitis of infants, due in most instances to thrush, is a definite entity with a probable high mortality rate and is more frequent in occurrence than generally realized.

GONCE JR., Madison, Wis.

THE VALUE OF THE HIPPURIC ACID TEST AND TAKATA-ARA REACTION IN THE INVESTIGATION OF HEPATIC DEFICIENCY. M. HENDERSON and B. SJLATT, M. J. Australia **1**:185 (Feb. 14) 1942.

Quick's hippuric acid excretion test is both a reliable and a sensitive index of hepatic function and is a valuable aid in estimating clinical progress, response to treatment and prognosis. It is simple to perform and devoid of danger to the patient but is not applicable to patients with poor renal function. The Takata-Ara test is practically valueless as a test of hepatic function and is not a specific test for hepatic disease. It is, however, a useful confirmatory test for disease of the parenchyma of the liver.

GONCE, JR., Madison, Wis.

THE DISTINCTION BETWEEN "SURGICAL" AND "MEDICAL" JAUNDICE BY THE EFFECT OF 2-METHYL-1, 4-NAPHTHOQUINONE (KAPILIN) ON THE PLASMA PROTHROMBIN. H. B. STEIN, South African M. J. **16**:12 (Jan. 10) 1942.

The effect of intramuscular injections of 2-methyl-1, 4-naphthoquinone (menadione) in 5 mg. doses on the plasma prothrombin was examined in 23 cases of jaundice. An effective response was associated with obstructive jaundice, while an ineffective response was obtained when there was hepatic damage. Provided, therefore, that the original prothrombin level is sufficiently low at the start, the nature of the response can be used to differentiate between obstructive and hepatocellular jaundice.

GONCE JR., Madison, Wis.

CHRONIC INTESTINAL INVAGINATION IN AN INFANT TWELVE MONTHS OF AGE. J. E. RIVAROLA and A. L. IBANEZ, Arch. argent. de pediat. **16**:355 (Oct.) 1941.

The authors report a case of chronic intestinal invagination in an infant 12 months of age. The condition had existed five weeks before operation and consisted in a complete invagination of the bowel with presentation of the invaginated portion at the anal orifice.

The infant had considerable diarrhea during most of the period of the invagination. At operation the invagination was reduced without the necessity of resection.

The infant made a complete recovery.

SCHLUTZ, Chicago.

THE TREATMENT OF BACILLARY DYSENTERY WITH SULFATHIAZOLE. J. M. VALDES and J. B. S. GALLARDO, Arch. argent. de pediat. **17**:3 (Jan.) 1942.

The authors report on the use of sulfathiazole in a number of cases of acute infectious diarrhea produced mainly by Gärtner's bacillus (Salmonella enteritidis) and by Flexner's bacillus (Shigella paradysenteriae). The results generally have been favorable. They recommended its use as early as possible in diarrheal conditions which are due to these organisms and which have not responded favorably to dietetic management.

SCHLUTZ, Chicago.

INTRAPERITONEAL INJECTION OF SULFONAMIDES IN CHILDHOOD. V. ZERBINO and A. NORBIS, Arch. de pediat. d. Uruguay **13**:37 (Jan.) 1942.

The authors believe that the use of intraperitoneal injections of sulfonamide drugs for children need not be limited to extraordinary occasions but feel that it constitutes an efficient technic in many cases of grave disorders. It has several advantages: 1. It is a harmless technic and well tolerated. 2. The drug is rapidly absorbed. For this reason it is a good technic for use when the situation is urgent. 3. It affords an extremely rapid diffusion of the drug, especially in the meningeal fluid. For this reason it is indicated in meningitis. 4. It permits the use of a large single dose, which is an advantage when it is desired to institute intensive treatment.

SCHLUTZ, Chicago.

Nervous Diseases

BRAIN METABOLISM: VIII. THE EFFECTS OF ELECTRIC SHOCK AND SOME NEWER DRUGS. S. BERNARD WORTIS, DONALD SHASKAN, DAVID IMPASTATO and RENATO ALMANSI, Am. J. Psychiat. **98**:354 (Nov.) 1941.

Wortis, Shaskan, Impastato and Almansi studied the effects of drugs on cerebral metabolism by two methods: The first consisted of injecting the drug in specified concentration into a white rat and after fifteen minutes removing the cerebral cortex, mincing it and studying respiration by the Barcroft-Warburg method for two hours. In the second method the cortex of a normal rat was immersed in Ringer's phosphate substrate both with and without dextrose and containing the drug in a specified concentration and the oxygen con-

sumption measured. The drugs studied consisted of acetylbetamethylcholine, epinephrine, physostigmine, morphine, picrotoxin, pilocarpine, prostigmine, tyramine, caffeine, cocaine, ergot, ergotoxine and nicotine. The injected drugs failed to affect the oxygen consumption of the brain in the dextrose substrate, but tyramine, picrotoxin and pilocarpine stimulated oxygen consumption in the sugar-free substrate. In the immersion experiment, epinephrine, caffeine, cocaine, ergotamine and ergotoxine inhibited the oxygen consumption in both the dextrose and the sugar-free substrate.

The authors studied the effects of electrically induced convulsions on brain metabolism by two methods: The first consisted of administering a single convulsive shock to a rat while the animal was still in coma, removing the brain and studying the respiration. This method showed that the total brain respiration is depressed in electrically convulsed animals. By the second method the authors induced a total of nine to fifteen convulsions in rats at a rate of two shocks per week. From three to thirty days after the last convulsion the brains were removed and studied in like manner. Again, the authors found that the metabolism of the brain was depressed in both the plain and the dextrose substrate, the depression being greater after repeated than after single shocks. Comparison of the effects of various forms of shock therapy on oxygen utilization by the brain tissue reveals that metrazol and camphor increase the respiratory metabolism of the tissue while electric convulsions interfere with brain respiration. Insulin interferes with cerebral respiration to a greater extent than does electric shock, the effect being due in a large part to the lack of dextrose.

FORSTER, Boston [ARCH. NEUROL. & PSYCHIAT.].

MENTAL DISORDER IN ONE OF A PAIR OF IDENTICAL TWINS. G. E. HOBBS, Am. J. Psychiat. **98**:447 (Nov.) 1941.

Five cases are presented. In every case 1 twin remained normal and the other showed abnormalities; as follows.

1. Twin B, 13 years old, has mental deficiency (intelligence quotient 57); twin A has an intelligence quotient of 109 and is slightly better developed physically. The condition in this case, the author believes, is probably due to birth injury, since twin B was delivered after a difficult labor.

2. Twin B, aged 19 years, has petit mal epilepsy and a psychosis. He was well until 8 years of age, when he began to have petit mal attacks. These were controlled by phenobarbital until he was 12 years of age. Psychotic symptoms appeared at 19 years following a minor accident on the farm. Twin A is well.

3. A 20 year old man of superior mentality had an onset epilepsy at 13 years of age. Birth followed a delayed delivery. The abnormality in this case is traceable to encephalitis following measles. The brother is well.

4. A woman 31 years of age had an affect depression. Recovery followed nine months of mental depression. Her sister is well.

5. A girl of 15 years had hysteria. She had fainting spells for six months but no true convulsions. The child was energetic and ambitious and worked hard at home and at school. Her twin sister, who has remained on the sidelines of such activities, has had no reaction.

JAHR, Omaha.

REGULATION OF THE TREATMENT OF EPILEPSY BY SYNCHRONIZED RECORDING OF RESPIRATION AND BRAIN WAVES. ROBERT S. SCHWAB, ALFRED GRUNWALD and WILLIAM W. SARGANT, Arch. Neurol. & Psychiat. **46**:1017 (Dec.) 1941.

The authors suggest the use of synchronous recording of respiration and brain waves as a method of regulating anticonvulsant drug therapy.

BEVERLY, Chicago.

SUSCEPTIBILITY TO CONVULSIONS IN RELATION TO AGE: I. INFLUENCE OF ACID FUCHSIN ON RATS OF VARIOUS AGE GROUPS. ALFRED FROLICH and I. ARTHUR MIRSKY, Arch. Neurol. & Psychiat. **47**:30 (Jan.) 1942.

The authors studied the susceptibility of rats of various ages to acid fuchsin and theophylline in an effort to find a reason for the susceptibility of young children and infants to convulsions. They found that acid fuchsin injected subcutaneously enters the nervous system of young rats and the animals have convulsions, the number being inversely proportional to age. It does not enter the nervous system of adult rats, and they do not have convulsions.

When theophylline is injected into adult rats, there is a change in their response to acid fuchsin so that they have convulsions when minute doses of the drug are injected intraperitoneally. The authors conclude that there is a "possibility that the increased liability of infants to convulsions may be due to the passage of toxic substances into the central nervous system."

BEVERLY, Chicago.

OBSERVATIONS ON PROTEINASE IN BRAIN. M. W. KIES and S. SCHWIMMER, J. Biol. Chem. **145**:685, 1942.

Brain proteinase has been partially purified and shown to be of the catheptic type. Dipeptidases and tripeptidases were found to be present in brain tissue. No evidence was obtained for the presence of a lipolytic enzyme, similar to the one previously reported in muscle. The results indicate the presence of a surprisingly large amount of cathepsin in brain as compared with muscle. Brain, however, autolyzes neither more rapidly nor to a greater extent than muscle under similar conditions. While the effect of the brain cathepsin undoubtedly contributes to the difficulty of handling brain tissue commercially, it does not seem to afford adequate explanation of the rapid disintegration of the material that is so frequently observed in the packing industry.

PAGE, Indianapolis [ARCH. NEUROL. & PSYCHIAT.].

BRAIN CEPHALIN, A MIXTURE OF PHOSPHATIDES. J. FOLCH, J. Biol. Chem. **146**:35, 1942.

The phosphatide fraction of brain called cephalin was formerly believed by some investigators to be a definite compound of glycerophosphoric acid with two molecules of fatty acids and one molecule of ethanolamine. Folch now adds that the individual phosphatides in such a fraction exhibit differences in their respective solubilities in mixtures of chloroform and alcohol. This fact is made use of for the separation from cephalin of three different fractions, namely, (*a*) phosphatidyl serine, (*b*) a compound which has the composition formerly attributed to the whole cephalin, and which is called phosphatidyl ethanolamine, and (*c*) a mixture of phosphatides, one or more of which contain inositol as a constituent. The fraction containing inositol phosphatide is less soluble in alcohol than either phosphatidyl serine or phosphatidyl ethanolamine; from it have been isolated, besides inositol, glycerophosphoric acid and serine, the presence of which indicates the probable presence of phosphatidyl serine in the mixture. Phosphatidyl ethanolamine, unlike the cephalin to which its composition was formerly assigned, is freely soluble in alcohol. From it have been isolated ethanolamine and glycerophosphoric acid. With the exception of phosphatidyl ethanolamine, the phosphatides in the cephalin fraction of brain lipids are strongly acidic and are isolated from brain as salts of potassium and sodium when treatment with mineral acid is avoided in the isolation. Treatment with hydrochloric acid removes the alkali cations. The method described for separating the phosphatides of cephalin is effective only when applied to material that has not had its mineral bases removed.

PAGE, Indianapolis [ARCH. NEUROL. & PSYCHIAT.].

A STRAIN OF VIRUS PRODUCING MENINGO-ENCEPHALOMYELITIS IN MICE, WITH SPECIAL REFERENCE TO PATHOGENESIS. LAWRENCE GAHAGAN and LEWIS D. STEVENSON, J. Infect. Dis. **69**:232 (Nov.-Dec.) 1941.

Gahagan and Stevenson describe a spontaneous meningoencephalomyelitis in mice produced by a filtrable virus. The disease is transmissible by intracerebral inoculation of a fresh or frozen suspension of brain or spinal cord of a recently paralyzed mouse, and the infective agent has not been recovered from mice paralyzed for more than nine days. It has not been transmitted by intranasal instillation of such material.

The lesions in the central nervous system produced by the disease include perivascular and diffuse infiltration of lymphocytes, gliosis, necrosis of ganglion cells, meningeal infiltration of lymphocytes and leptomeningeal hemorrhage.

TOOMEY, Cleveland.

INFECTION OF MICE BY FEEDING WITH TISSUES CONTAINING THE VIRUS OF ST. LOUIS ENCEPHALITIS. C. G. HARTFORD and J. BRONFENBRENNER, J. Infect. Dis. **70**:62 (Jan.-Feb.) 1942.

When either laboratory mice or wild mice were allowed to feed on the bodies of newly born mice dead or moribund from experimental infection with the virus of St. Louis encephalitis, some of them acquired encephalitis due to the virus. Of those that survived, latent infection was indicated in some by the existence of relative specific resistance to intracerebral injection of the virus. Subclinical infection was also demonstrated in 2 cases directly by the detection of the virus in the spleen. It has been found that the use of infected bodies of newly

born mice was more effective in the production of encephalitis by feeding than when infected adult brain tissue was employed, but the reason for this was not determined.

TOOMEY, Cleveland [AUTHORS' SUMMARY].

REPORT OF A CASE OF PNEUMOCOCCUS TYPE XVIII MENINGITIS COMPLICATED BY SO-CALLED "SILENT MASTOID." JAMES M. DOBBINS and MICHAEL A. BRESCIA, New York State J. Med. **41**:2245 (Nov. 15) 1941.

A boy 8 months of age had right-sided convulsions and meningitis. Cultures of the spinal fluid revealed pneumococci of type XVIII, and the same organisms were recovered from the blood. The child received adequate chemotherapy. Paracentesis was performed on the right ear, and it was followed later by a mastoidectomy. This mastoid was found to be normal. Roentgenograms showed the other mastoid to be normal, but at autopsy extensive mastoiditis was found.

AIKMAN, Rochester, N. Y.

PNEUMOCOCCAL MENINGITIS: RECOVERY WITH SULPHATHIAZOLE. STEPHEN J. HOWARD, Lancet **2**:512 (Nov. 1) 1941.

This is a report of a case of meningitis due to pneumococci of type II in a 1 year old boy, who was successfully treated by oral administration of sulfathiazole.

LANGMANN, New York.

PFEIFFER'S BACILLUS MENINGITIS: RECOVERY WITH CHEMOTHERAPY. N. M. JACOBY, Lancet **2**:753 (Dec. 20) 1941.

Jacoby reports the recovery of a 1 year old infant who was admitted to the hospital with a twenty-four hour history of profuse vomiting, rigidity of the body, fixed stare and drowsiness. He was extremely ill; he had a temperature of 104 F. and some nuchal rigidity, but Kernig's sign was not elicited. The spinal fluid was turbid, with 0.2 per cent of protein, 1,600 polymorphonuclear leukocytes and 100 lymphocytes per cubic centimeter. Direct smears showed gram-negative bacilli of hemophilus type. Culture gave a pure growth of Haemophilus influenzae.

Sulfapyridine was given by mouth for seven days (total dose 17 Gm.). The temperature remained normal after twenty-four hours. At the end of four days all symptoms had disappeared.

No claim is made that the recovery was due to chemotherapy; it may have been fortuitous. Only one lumbar puncture was done, a procedure that the author has followed in all cases of meningitis since chemotherapy has proved so effective.

LANGMANN, New York.

THROMBOCYTOSIS WITH STAPHYLOCOCCIC MENINGITIS TREATED WITH CHEMOTHERAPY. R. V. DIAZ and F. B. HERNANDEZ, Bol. Soc. cubana de pediat. **13**:453 (Nov.) 1941.

The authors report a case of thrombocytosis with staphylococcic meningitis in a child 5 years old. The patient was treated with massive doses of sulfathiazole, given both intravenously and orally. Rapid regression of the process and of the symptoms occurred.

The authors suggest that along with oral therapy intravenous therapy should always be used in the treatment of this condition.

SCHLUTZ, Chicago.

POLYNEURITIS FOLLOWING THERAPY WITH A SULFONAMIDE COMPOUND. ADHERBAL TOLOSA and CARLOS V. SAVOY, Sąo Paulo med. **12**:269, 1939.

Tolosa and Savoy discuss the sulfonamide compounds, their uses and contraindications, and relate a case of acute gonorrhea treated with dimethylsulfanilylsulfanilamide (N1, N1-dimethyl-N4-sulfanilylsulfanilamide). A total of 40 Gm. was given in thirteen days to a youth aged 18. About a week after cessation of the treatment the patient began to lose strength in his legs and to walk unsteadily and soon was bedridden. He had the sign of polyneuritis with tenderness of the calves, muscular weakness and absence of the achilles reflex. He was given injections of strychnine and vitamin B_1, massage and galvanotherapy. After five months he began to improve slowly. The authors note other cases of polyneuritis provoked by this drug which have been reported in the medical literature.

BAILEY, Chicago [ARCH. NEUROL. & PSYCHIAT.].

OXYCEPHALIA IN ONE OF A PAIR OF TWINS. EYVIND EK, Svenska läk.-tidning. **38**:2881 (Dec. 24) 1941.

This is a report of a typical case of oxycephalia in a somewhat psychically retarded and epileptic biovular male twin aged 9 years. The other twin, who in all other respects was normal, displayed a slight oxycephalia, and so did the father.

WALLGREN, Göteborg, Sweden.

Psychology and Psychiatry

POPULARITY AMONG PRESCHOOL CHILDREN. ROSEMARY LIPPITT, Child Development **12**:305 (Dec.) 1941.

The paired comparison method was administered to 45 preschool children (three groups attending the Iowa Child Welfare Research Station preschools) to obtain the popularity ranking of each child from his fellow preschool mates. By the same method the teacher estimated the popularity of each child. Numerous observations and tests obtained for each subject revealed that no one measure was highly indicative of child popularity. However, cooperation in school routines seemed to indicate that the popular child tended to show quick unobtrusive adjustment while the reverse was true of the unpopular child. Measures related to popularity in one or more of the groups, but not in all three, were: constructive behavior in the play situation and in the face of failure and the amount of hostile and friendly social behavior the child manifested and experienced from others. The measures related to the teachers' estimate of child popularity were: the amount and intensity of social participation, the amount of compliant behavior the child manifested and experienced, the amount of directing behavior, the number of times the child was refused by others and the amount of child-child communication. Unrelated to either measure of popularity were: emotional reaction in the face of failure, paper cutting ability, gross motor ability, the number of days the child attended school during the semester of the study, mental age, intelligence quotient and oral nervous habits.

FROM THE AUTHOR'S SUMMARY.

THE LOCATION OF THE SUBORDINATE CLAUSE IN ORAL AND WRITTEN LANGUAGE. EDITH A DAVIS, Child Development **12**:333 (Dec.) 1941.

A comparison is made between the oral speech of children at 5½ and 9½ years of age, and observations of Fritz and Grace Heider, who analyzed composition of deaf children, and of P. P. Bushnell, who studied oral and written compositions of tenth grade pupils. In both oral and written language, clauses of time and condition tend to precede or interrupt the main clause, and placing the subordinate clause early in the sentence seems to be related to the degree of linguistic maturity. The tendency to express or omit the connective in relative and object clauses, and the use of indirect discourse are discussed in the light of the Heiders' findings. Analysis of specimen compositions by Bushnell indicates that the index of subordination is higher in written than in oral language. FROM THE AUTHOR'S SUMMARY.

VARIATIONS IN PULSE AND RESPIRATION DURING DIFFERENT PHASES OF INFANT BEHAVIOR. H. M. HALVERSON, J. Genet. Psychol. **59**:259 (Dec.) 1941.

This study conducted at the Yale Clinic of Child Development is concerned with respiratory and cardiac rate and rhythm in situations normally arising in an infant's daily life.

The physiologic state of the infant was revealed by his breathing. Each type of behavior in various situations has its characteristic breathing pattern.

Unisonal breathing occurs during satiation. When excitement occurs the thoracic and abdominal breathing is directly proportional in frequency and depth to the excitement; ultimately the breathing becomes exclusively costal and then unisonal as the excitement abates.

During nursing the pulse rate increases and the respiratory rate decreases.

The number and degree of alterations of respiratory curves are minimum during sleep and maximum during crying.

There is no normal pulse or respiratory rate for infants in general or for the individual infant. The high frequency, irregularity and easy irritability of the pulse in early infancy raise a question as to the completeness of the inhibitory apparatus.

There is a close correspondence between pulse rate and respiratory rate in different situations. As a rule irregularities in breathing and fluctuations in pulse rate are coincidental.

Moderate and extreme types of Cheyne-Stokes breathing occurred during sleep. The moderate type was also exhibited when infants were awake and quiet.

Hiccups occur during inspiration or expiration and have little or no effect on the breathing or pulse rate.

No relation was found between age and size and pulse rate or respiratory rate.

WEINFELD, Highland Park, Ill.

THE IMMATURE CHILD. ERICH BENJAMIN, Nervous Child, 1941, no. 1, p. 2.

The author describes immaturity or lack of emotional development or regression in children and concludes that "environment plays an important part in the origin of such distur-

bances." Giving the child the best opportunity for his further development is the treatment to follow. The article is too vague to be of value.

BEVERLY, Chicago.

PREVENTIVE MENTAL HYGIENE IN CHILDHOOD. C. M. LOUTTIT, Nervous Child, 1941, no. 1, p. 43.

The writer discussed the importance of prophylaxis in the field of mental hygiene and outlined a method of approach in the home, the school and the community. The biologic and psychologic factors in behavior were considered. It is a general article, conservative and logical.

BEVERLY, Chicago.

CHILD GUIDANCE TWENTY YEARS AFTER. BERNARD GLUECK, Nervous Child, 1941, no. 1, p. 60.

This is an excellent article discussing the general psychiatric problems of today and their relationship to child guidance. Glueck warns against giving up the progress in child guidance during the emergency.

BEVERLY, Chicago.

THE MOOSEHEART SYSTEM OF CHILD GUIDANCE. MARTIN L. REYMERT, Nervous Child, 1941, no. 1, p. 73.

This is a description of the program at the Mooseheart, Ill., child-rearing center. The cottage plan, educational program and general principles of child rearing are discussed. The article contains much valuable information relative to progressive attitudes toward children.

BEVERLY, Chicago.

COMMUNITY SUPERVISION OF MENTAL DEFECTIVES IN MASSACHUSETTS. NEIL A. DAYTON and MARION A. NUGENT, New England J. Med. **225**:941 (Dec. 11) 1941.

For many years mentally defective children have been referred to as "institutional problems." This belief has come into being since 1848, when the first state school was opened in Massachusetts.

During the last fifteen years, however, another type of community supervision has come into being. The overcrowding of the three state schools has made it impossible for children seeking admission to receive the desired training in such a school. Complicated social problems and difficult home situations have been observed for many of these children. In this state of affairs it has become necessary that the Department of Mental Health take some means to offer at least temporary relief.

The patients under the supervision of the department fall into six general groups:

1. Home training group: The home training children are the youngest. They include children of preschool or school age, with mental ages from 2 years or less to about 6 years. Because of their low mentality, these children have been refused admission to school or have been excluded from regular classes or special classes.

2. Special class group: The special class group comprises children now being cared for within the public school system.

3. Training home group: Subjects placed in training homes prior to wage placement are made up of girls 17 to 25 years of age who have reached their capacity in regular class or special class work. Their intelligence quotients range from 58 to 69.

4. Wage earning group: The subjects who are wage earning have comprised the largest group of supervisioned patients since the beginning of the division. They receive room, board and wages commensurate with their ability. Some have begun with wages as low as $1.00 a week and progressed to $8.00 a week. The average wage is between $3.00 and $4.50 a week. Experience with the wage-earning group has taught that mental defectives with supervision can be influenced to carry on in the community as responsible, self-supporting citizens. Without guidance, they are easily swayed by doubtful influences and may become community liabilities rather than assets.

5. Family care group: The boarding-out or family care patients have been placed by the division since 1938, when funds were appropriated for this purpose. If the patient is committed to the department, the state pays the board. If the commitment is voluntary, the board is paid by relatives. In either event, the social worker investigates possible homes and selects the one considered most suitable for the patient.

6. General supervision and consultation group: The general supervision and consultation subjects are referred by various public and private agencies as well as by individuals. The

patients under general supervision are often older boys and girls who do not fit into any of the other five groups. Usually they are being cared for in their own homes.

At the end of 1940, a total of over 54,000 mental defectives were known to the Department of Mental Health, through its Central Registry of Mental Defectives. Over 4,000 new cases of mental deficiency are being discovered each year. The authors believe that institutionalization should be the last thought, after all other resources have been exhausted.

GENGENBACH, Denver.

PERCENTILES FOR INTELLIGENCE QUOTIENTS. PATRICK SLATER, Lancet **1**:101 (Jan. 24) 1942.

The purpose of this article is to explain why psychologists would like to discard the intelligence quotient, why physicians should be prepared to let it be discarded and what sort of scale should take its place.

An intelligence quotient is, as stated, the ratio between mental age and chronologic age. But mental age abstracted from chronologic age is an inept fiction. The psychologic picture of a bright child of 6 is entirely different from that of a dull child of 13, though his "mental age" may be the same. To assign them both a mental age of 9 is a solecism.

Physicians need psychologic tests particularly for differentiating defective children, backward children and precocious children who are found respectively in the bottom 1 per cent of the population, the bottom 10 per cent and the top 5 per cent approximately. The first, the tenth and the ninety-fifth percentile define the limits within which these types of children fall on a percentile scale. The intelligence quotient do not define these limits reliably, since their distributions vary.

LANGMANN, New York.

Diseases of the Genitourinary Tract

RUPTURED RIGHT KIDNEY. Case Rep., Children's Mem. Hosp. **1**:13 (Jan.) 1942.

Traumatic rupture of the right kidney was treated conservatively. At the time of the report, recovery was progressing nicely. Methods of diagnosis and treatment are discussed.

DUSHANE, Evanston, Ill.

OCCURRENCE OF URINARY CALCULI IN INBRED STRAIN (C_3H) OF MICE TREATED WITH ESTROGEN. JOHN R. SCHENKEN, EDWARD L. BURNS and WILLIAM M. MCCORD, Endocrinology **30**:344 (Feb.) 1942.

Urinary calculi composed of calcium and magnesium phosphates were found in a high percentage of male rats which had been given eight to twenty weekly injections of 100 rat units of estrogen (alpha estradiol benzoate in sesame oil). JACOBSEN, Buffalo.

EMOTIONAL GLYCOSURIA IN MEDICAL AND DENTAL STUDENTS. E. GREEN and F. E. EMERY, Endocrinology **30**:353 (Feb.) 1942.

From these studies on medical and dental students it appears that considerable sugar in the urine associated with the emotional excitement of written examinations is not common, occurring in less than 2 per cent of 244 subjects. JACOBSEN, Buffalo.

THYMOMA IN MYASTHENIA GRAVIS. BARNES GILLESPIE, Arch. Path. **32**:659 (Oct.) 1941.

Weigert first describes tumor of the thymus gland in cases of myasthenia gravis, and since then 58 cases have been recorded. In a typical case of myasthenia gravis reported by Gillespie microscopic examination of the thymus revealed a small tumor showing benign epithelial hyperplasia. He subscribes to the theory that the thymic tumor liberates a hormone which acts at the myoneural junction to destroy acetylcholine.

WINKELMAN, Philadelphia [ARCH. NEUROL. & PSYCHIAT.].

Diseases of the Ductless Glands; Endocrinology

A DIABETES INSIPIDUS-LIKE CONDITION PRODUCED BY SMALL DOSES OF DESOXYCORTICOSTERONE ACETATE IN DOGS. MICHAEL G. MULINOS, CLIFFORD L. SPINGORN and MARY E. LIPKIN, Am. J. Physiol. **135**:102 (Dec.) 1941.

A syndrome of polydipsia and polyuria was produced in 5 normal female dogs by the daily injection of desoxycorticosterone acetate (DCA) in doses of 2 and 4 mg. The period of injection varied from twelve to one hundred and eighty days in different dogs, and the substance was well tolerated except for the increased fluid exchange. NOURSE, Cleveland.

CREATINURIA INDUCED BY METHYL TESTOSTERONE IN THE TREATMENT OF DWARFED BOYS AND GIRLS. LAWSON WILKINS, WALTER FLEISCHMANN and JOHN E. HOWARD, Bull. Johns Hopkins Hosp. **69**:493 (Dec.) 1941.

Methyl testosterone by mouth was given to 5 dwarfed, sexually undeveloped boys. Nitrogen retention was observed in three days, and in 10 days there was an increase in the output of creatine. When the use of methyl testosterone was discontinued the creatinuria decreased gradually. According to other observers testosterone propionate administered intramuscularly does not result in nitrogen retention or increased creatinuria. LYTTLE, New York.

EFFECT OF THYROID AND THYROTROPIC HORMONES UPON OXYGEN CONSUMPTION (QO_2) OF THE THYROID OF THE GUINEA PIG. CARLOS GALLI-MAININI, Endocrinology **29**:674 (Nov.) 1941.

The oxygen consumption of thyroid tissue of guinea pigs immersed in a medium containing the material to be tested can be measured. Experiments reported in this article indicate that thyrotropic hormone increased the oxygen consumption of thyroid tissue and that thyroid hormone reduced it. Thyrotropic hormone is inhibited in vitro by thyroglobulin. Its stimulating action is nullified if the right amount of thyroid hormone is added to the medium. The hypothesis is advanced that circulating thyroid hormone acts as a regulator of activity of the thyroid gland, independent of the inhibiting effect of thyroid hormone on thyrotropic hormone production by the pituitary. JACOBSEN, Buffalo.

THE RELATION OF THE THYROID AND THE PITUITARY GLANDS TO IODINE METABOLISM. ASHER CHAPMAN, Endocrinology **29**:680 (Nov.) 1941.

Response of the thyroid glands of hypophysectomized and intact rats maintained on high and low iodine diets was found to be similar.

It is concluded from the evidence presented here that the thyroid gland is able to respond to the stimulus of a low intake of iodine in the absence of the pituitary.

JACOBSEN, Buffalo.

EXTRATHYROIDAL IODINE METABOLISM. ASHER CHAPMAN, Endocrinology **29**:686 (Nov.) 1941.

Most studies on iodine metabolism have focused attention on the intimate relation that exists between iodine and the thyroid. Recently the extrathyroidal production of thyroxin or thyroxin-like substances from the iodization of protein has been accomplished. In view of this fact a study of the effect of iodine on a completely thyroidectomized animal was carried out.

It was found that a difference in iodine level in the diets of thyroidectomized rats significantly altered the changes in weight and surface area, the water intake, the food utilization and the metabolic rate. These changes were not induced in the intact animals by deprivation or administration of iodine.

From the data presented it is concluded that iodine may play a role in body metabolism in the absence of thyroid tissue, possibly by the production of a thyroxin-like substance in the tissues. JACOBSEN, Buffalo.

EPIPHYSEAL GROWTH: THE EFFECT OF REMOVAL OF THE ADRENAL AND PITUITARY GLANDS ON THE EPIPHYSES OF GROWING RATS. THEODORE H. INGALLS and DONALD R. HAYES, Endocrinology **29**:720 (Nov.) 1941.

The authors studied the effects of both hypophysectomy and adrenalectomy on the epiphyses of rats, using roentgenograms and silvered sections of bone as well as the usual histologic preparations.

It was found that the normal functioning of the adrenal gland is as essential for continued growth of the epiphysial plate of the rat as is the normal functioning of the hypophysis. It is suggested that the atrophy of the adrenal cortex which has been shown to occur after hypophysectomy may be a major factor in the interruption of growth which also follows that procedure. JACOBSEN, Buffalo.

CONDITIONS INFLUENCING THE COURSE OF STEROID HORMONE ANESTHESIA. HELEN WINTER, Endocrinology **29**:790 (Nov.) 1941.

It has been found recently that steroid hormones produce anesthesia when injected intraperitoneally or intravenously. All observations concerning this action of the steroids are in

agreement with what has been called the "fundamental law of steroid hormone anesthesia," namely, that all steroid compounds having a hormone action are capable of producing anesthesia while no steroid compound devoid of such action possesses this power.

In a study of this phenomenon in rats the following observations were made:

"Female rats are more sensitive to the anesthetic action of progesterone than males but this sex difference is obvious only after maturity. The normal endocrine activity of the testis is largely, if not entirely, responsible for this comparative resistance of the males since castration increases sensitivity in males but is without effect in female rats. Conversely the resistance of castrate males and females may be raised by methyl testosterone administration.

"Treatment with glucose [dextrose] and adrenalin [epinephrine] tends to increase, while treatment with insulin and exposure to excessive heat or cold tends to decrease the resistance of the rat to the anesthetic action of progesterone."

JACOBSEN, Buffalo.

BIOASSAY OF THE GROWTH HORMONE OF THE ANTERIOR PITUITARY. WALTER MARX, MIRIAM E. SIMPSON and HERBERT M. EVANS, Endocrinology **30**:1 (Jan.) 1942.

This paper reports ways for further standardizing and improving the "increase in body weight of rats" method of assaying the pituitary growth hormone.

JACOBSEN, Buffalo.

GONADOTROPIC HORMONE IN AP OF MALE AND FEMALE RABBITS DURING GROWTH. A. J. BERGMAN and C. W. TURNER, Endocrinology **30**:11 (Jan.) 1942.

A study is reported concerning the amount of gonadotropic hormone in the pituitaries of groups of male and female New Zealand white rabbits of increasing body weight. This was measured by the increase of gonad weight of baby chicks. There were a gradual rise and then a uniform level throughout reproductive life and a notable decrease indicating the climacteric. The gonadotropic hormone concentration of the anterior lobe of the pituitary gland of sexually mature males averaged about 70 per cent above that of females of comparable weight.

JACOBSEN, Buffalo.

A STUDY ON THE SPECIFICITY OF THE ANTI-INSULIN EFFECT. H. JENSEN, J. F. GRATTAN and G. W. HART, Endocrinology **30**:203 (Feb.) 1942.

In rabbits and mice various urinary preparations produced elevation of the blood sugar but did not increase the glycogen content of the liver, whereas certain pituitary principles eliciting a similar effect on the blood sugar level also promoted deposition of glycogen in the liver.

JACOBSEN, Buffalo.

THE EFFECT OF THYROIDECTOMY ON LACTATION IN THE ALBINO RAT. DAVID KARNOFSKY, Endocrinology **30**:234 (Feb.) 1942.

Thyroidectomy causes a diminution in lactation of rats. There is evidence that this is due to effects on the pituitary gland affecting the formation of prolactin. Thyroid replacement therapy seems to increase lactation.

JACOBSEN, Buffalo.

EFFECT OF THE GONADOTROPIC SUBSTANCE OF PREGNANT MARE'S SERUM ON THE BLOOD PLASMA-ASCORBIC ACID OF THE BOVINE. RALPH E. ERB and FREDERICK N. ANDREWS, Endocrinology **30**:258 (Feb.) 1942.

Injection of 2,250 rat units of a chorionic gonadotropin from the serum of pregnant mares into bulls and cows caused a decrease of from 20 to 67 per cent in the ascorbic acid level of the plasma of venous blood. Recovery to preinjection levels required eight days or longer.

JACOBSEN, Buffalo.

EFFECT OF CRYSTALLINE ESTRIN IMPLANTS ON THE PROXIMAL TIBIA AND COSTOCHONDRAL JUNCTION OF YOUNG FEMALE RATS. MIRIAM E. SIMPSON, EDWIN A. KIBRICK, HERMANN BECKS and HERMAN M. EVANS, Endocrinology **30**:286 (Feb.) 1942.

Various differences in amount and distribution of osseous tissue were noted after subcutaneous implantation of pellets of alpha estradiol dipropionate in rats.

JACOBSEN, Buffalo.

DOES ESTROGEN SUBSTITUTION MATERIALLY INHIBIT PITUITARY GONADOTROPIC POTENCY? CARL G. HELLER, EMILY J. HELLER and ELMER L. SEVRINGHAUS, Endocrinology **30**: 309 (Feb.) 1942.

It is the generally accepted belief that the gonadotropic action of the pituitary gland is entirely regulated by the secretions of the gonads and, more specifically, that the estrogenic hormones exert an inhibitory or depressant effect on the gonadotropic action of the hypophysis. The experiments on rats here reported led the authors to the conclusion that estrogens in amounts that already overstep the physiologic bounds necessary for some organs do not decrease pituitary potency in rats or excretion of gonadotropin by menopausal females.

JACOBSEN, Buffalo.

FETAL RAT PARATHYROIDS AS AFFECTED BY CHANGES IN MATERNAL SERUM CALCIUM AND PHOSPHORUS THROUGH PARATHYROIDECTOMY AND DIETARY CONTROL. JOHN G. SINCLAIR, J. Nutrition **23**:141 (Feb.) 1942.

Fetal rat parathyroids at birth were found by Sinclair to weigh 2.8 mg. per kilogram of body weight, which is about double the ratio in adult rats. A diet balanced in calcium and phosphorus content failed to prevent enlargement of the parathyroids during pregnancy, with cumulative effects in a second pregnancy. Both maternal and fetal parathyroids were suppressed when the mother was fed a diet containing more calcium and less phosphorus, but this diet gave superior results after parathyroidectomy. An excess of maternal serum calcium or an excess of maternal parathyroid hormone depressed the fetal parathyroids. With a subnormal maternal serum calcium level or excess of serum phosphorus the fetal parathyroids were stimulated. The fetal parathyroid, which is about 5 per cent of the adult size, was found inadequate to protect the mother against the results of parathyroidectomy.

FREDEEN, Kansas City, Mo.

DIABETES INSIPIDUS IN ONE OF TWINS. HARRY BLOTNER, New England J. Med. **225**:946 (Dec. 11) 1941.

According to some observers diabetes insipidus is associated with a hereditary or familial tendency. The author has been fortunate in observing for the last seven years a pair of nonidentical twins, one whom has this disease. The boy, 18½ years old at the time of the report, showed symptoms of diabetes insipidus at 5½ years. His sister, whose past history was entirely normal, was about a head taller and 25 pounds (11.3 Kg.) heavier than the boy. Photographs are shown of the twins when they were 8 and again when they were 14 years old, illustrating the difference in the rapidity of their growth. Roentgenograms of the right hand of each at 17 years are also shown; the hand of the girl shows normal development and ossification while in that of the boy the epiphyses are still open, which indicates a disturbance in the anterior lobe of the pituitary gland. The urinary output of the boy, which has gradually increased, is now 9 to 10 liters, but it has always dropped to normal with the intranasal or intramuscular administration of pituitary extract. GENGENBACH, Denver.

CUSHING'S DISEASE. F. S. P. VAN BUCHEM, Acta med. Scandinav. **108**:544, 1941.

Van Buchem presents a report of a case of Cushing's disease observed for eight years. Progressive osteoporosis of vertebrae and ribs developed, but the long bones remained normal. This osteoporosis differed from that seen in hyperparathyroidism in that it was not universal, osteoclasts were rare, there was an osteoid margin around the thin spicules of bone and the bone marrow did not show fibrotic changes. The author states without giving actual data that there was increased calcium excretion in the stools but not in the urine. Serum calcium did not rise above 11 mg. per hundred cubic centimeters. The carbohydrate tolerance was diminished. The patient twice was operated on for renal calculi. At autopsy the parathyroids were found histologically normal. Unfortunately, the adrenals, which appeared normal on gross examination, were not examined under the microscope. The hypophysis revealed a cyst and a 3 by 6 mm. solid tumor in the pars anterior. The tumor consisted of basophilic cells, some of which showed the hyaline degeneration described by Crooke. The posterior part was atrophied.

KAJDI, Baltimore.

CASE OF LAURENCE-MOON-BIEDL SYNDROME. SIGURD WENDT, Nord. med. (Hygiea) **12**:2840 (Oct. 4) 1941.

The patient, a boy of 10 years, was the third of four children; the other three were normal. He had the characteristic features of the syndrome: adiposity, hypogenitalism, mental

retardation and retinitis pigmentosa with impaired vision. There was no polydactylia. Wendt had the opportunity to examine another boy whose case had previously been reported from Sweden by von Bahr and Normark. This boy was now 13½ years of age. He had shown a decreased basal metabolism (—20 per cent) and therefore had been treated with thyroid during the last three years. He was now of ordinary height and weight, and his secondary sexual organs were normally developed.

WALLGREN, Göteborg, Sweden.

THE FUNCTION OF THE THYROID GLAND IN PREMATURE INFANTS. GRETE GÖRTZ, Ugesk. f. læger **103**:884 (July 3) 1941.

It was not possible to demonstrate any hypofunction of the thyroid gland in premature infants by means of determinations of blood cholesterol. Histologic examinations of the thyroid gland from 3 premature infants who died shortly after birth gave evidence of hypofunction.

WALLGREN, Göteborg, Sweden.

Diseases of Muscles, Bones, Joints and Lymph Glands

EOSINOPHILIC GRANULOMA OF BONE. ARTHUR S. THURM, Bull. Hosp. Joint Dis. **3**:9 (Jan.) 1942.

A case of eosinophilic granuloma affecting several bones of the body (viz., both femurs and four ribs) is described. Only two of the six lesions (one of a femur and one of a rib) produced symptoms. They were associated during the early weeks of the course of the disease with a low grade fever, a moderate leukocytosis and a moderately increased sedimentation rate but no eosinophilia. The lesions showed evidence of a tendency to healing spontaneously (eleventh rib, right) as well as after simple curettage (right femoral neck).

AUTHOR'S SUMMARY.

SEPTIC KNEE AND SEPTIC ANKLE: THE ROLE OF SULFONAMIDE DRUGS IN THEIR TREATMENT. Case Rep., Children's Mem. Hosp. **1**:11 (Jan.) 1942.

Sulfathiazole was used in the treatment of 2 patients with septic arthritis. The affected joint of one of the patients was incised, and recovery ensued in one week; the treatment of the other was entirely conservative, and the course of the disease was ten days.

DUSHANE, Evanston, Ill.

SOFT SWELLINGS IN THE LEFT SIDE OF THE NECK AND LEFT ARM IN AN INFANT. Case Rep., Children's Mem. Hosp. **1**:14 (Jan.) 1942.

The case of a 13 month old boy with multiple lymphangiomas is presented. Treatment with radium was ineffective, but injection of sclerosing fluids resulted in improvement.

DUSHANE, Evanston, Ill.

THE INTERRELATIONSHIP OF MANGANESE, PHOSPHATASE AND VITAMIN D IN BONE DEVELOPMENT. G. F. COMBS, L. C. NORRIS and G. F. HEUSER, J. Nutrition **23**:131 (Feb.) 1942.

Combs and associates conclude that there is an intimate relationship between the phosphatase activity of the bones and the manganese content of the diet. By omitting manganese from the rachitogenic diet of chicks, the bone phosphatase was reduced to normal level. Thus, in manganese deficiency, with the lowering of the phosphatase level bone development was retarded, with resulting shortened bones, the ash content was reduced and the strength of the union between epiphysis and diaphysis was greatly reduced.

FREDEEN, Kansas City, Mo.

CONGENITAL DEFORMITIES IN THE REGION OF THE FORAMEN MAGNUM: BASILAR IMPRESSION. W. T. PEYTON and H. O. PETERSON, Radiology **38**:131 (Feb.) 1942.

Anomalies of the bony structures (basilar impression, platybasia and basilar invagination) about the foramen magnum may produce many neurologic signs. While variable, they consist principally of irritation and paralysis of the cervical nerves and spinal cord tracts, irritation and paralysis of the cranial nerves in the posterior fossa, disturbance of the cerebellum and medulla oblongata and an increase in intracranial pressure. The skeletal signs consist of a short neck with the head shifted downward between the shoulders and tilted backward with restriction in movement of the head and neck. Numerous syndromes result from these anomalies and mistaken diagnoses of syringomyelia and multiple sclerosis have been made.

Basilar impression consisting of a combination of severe grade anomalies of the occipital bone and upper cervical vertebrae is a rare lesion. In a typical specimen the cervical portion of the spine appears to have been pushed up into the base of the skull. Roentgenograms of the base of the skull and the cervical portion of the spine will demonstrate all of the gross bony anatomic variations. The posterior arch of the first cervical vertebra is absent, and the odontoid process occupies a somewhat posterior position. Some degree of assimilation of the atlas in which the posterior arch is fused with the occipital bone is present in lateral views in all cases. However, the author found it impossible to demonstrate satisfactorily a synostosis at the atlanto-occipital joint; also the shortness of the neck and the difficulty experienced in flexing the neck, together with the existing deformity of the foramen magnum, make unsatisfactory films of this region in all projections excepting the lateral views. Of the patients whose cases are reviewed, including the author's 3, all were adults, with the exception of 3 whose symptoms began at the ages of 12, 15 and 16 years.

When neurologic symptoms are present, a suboccipital craniotomy and laminectomy of the upper cervical vertebrae should be performed. Cases in which such an operation has been performed are as yet too few to enable one to evaluate the results. If it is found that an operation will prevent progression of a condition which is frequently fatal, even if extensive restoration of lost function is not obtained, surgical intervention will remove the hopeless attitude that basilar impression is an interesting lesion for which nothing can be done.

ANSPACH, Chicago.

TREATMENT OF RHEUMATOID ARTHRITIS IN CHILDREN. DERMOT RODEN, Brit. M. J. **1**:102 (Jan. 24) 1942.

Because of the many remedies now in use for the treatment of rheumatoid arthritis the author briefly reviews the various treatments.

1. *Focal Infection.*—It is advised that all obviously infected foci should be remedied. However, indiscriminate surgical intervention should be condemned, and it is advocated that the general physician and not the "focal specialist" should be the person deciding on what foci should be removed.

2. *Vaccines and Filtrates.*—Concerning the use of vaccines and filtrates, the author feels that they are of little value. Quoting an editorial comment in the sixth *Rheumatism Review* (1940), he says: "It is difficult to understand why vaccines should be expected to cure this disease of unknown origin when no infectious disease of known aetiology is cured by vaccine."

3. *Foreign Proteins.*—Foreign protein therapy has been shown to yield some good results in rheumatoid arthritis. However, it is felt that too drastic a treatment is unjustified.

4. *Diet, Vitamins and Transfusion of Blood.*—Since these are grouped in the general class of supportive measures, it is certainly indicated that all of these types of therapy should be used.

5. *Gold Salts.*—Because of the dangerous toxic effects of gold salts many investigators have condemned their use. The author feels that gold salts are of value, but when they are administered the patient should be watched carefully for toxic effects. Roden advocates their use in cases of active rheumatoid arthritis.

6. *Artificial Jaundice.*—Many workers have noted that attacks of jaundice greatly improve an arthritic patient. Because of the difficulty of producing artificial jaundice without too great a damage to the liver, this treatment is not recommended.

7. *Physical Therapy.*—It is generally agreed by all physicians that the use of physical therapy is of value. The author feels wholeheartedly that it is advantageous.

Two cases are reported in which the use of the types of therapy discussed was tried. The results were gratifying. In his summary the author states that the disease tends to "burn itself out" before the child reaches 16 years of age. He also thinks that all treatment should be carried out concurrently rather than singly and that the best results are obtained by employing physical therapy over a prolonged period with the injection of gold salts. In his cases the injection of a mixture of bilirubin and bile salts to help his patients was disappointing.

BIRDSONG, University, Va.

STILL'S DISEASE. J. B. BURT, Proc. Roy. Soc. Med. **35**:86 (Dec.) 1941.

A case of Still's disease in a boy of 9 years is reported. On his admission to the hospital there were swelling, heat and redness of the fingers, wrists, elbows, ankles and knees. There was also subluxation of the right hip which recovered after weight extension for twenty days. The treatment given was rest and the use of plaster rest splints. Sodium gold thiomalate was given in 0.01 Gm. doses for a total dose of 0.07 Gm. On the patient's readmission to the

hospital great improvement was noted. He was walking and had no pain except slight pain in the right knee. There was a tendency to eversion of the right foot. The hematocrit reading was 38 per cent; formerly it had been 33 per cent. The suspension stability (corrected) was 62 per cent (formerly, 65 per cent). Points of special interest in the case are as follows: (*a*) the value of gold treatment for Still's disease; (*b*) the subluxation of the right hip due to weakness of muscles and complete restoration within twenty days by weight extension.

WILLIAMSON, New Orleans.

MYOTONIA CONGENITA ATROPHICA: STUDY OF A FAMILY. F. QUIROS M. and E. GARCIA CARRILLO, Rev. mex. de psiquiat. **9**:15, 1942.

This is a study of the only family with myotonia to be reported from Costa Rica. Endocrine disturbances were frequent, as well as alopecia and cataract. The mother of the present family was myotonic. The maternal grandfather was not myotonic but had cataracts. In the present family 3 men, aged 26, 28 and 30, are myotonic. One woman is married and sterile and suffers from urticaria and Quincke's edema but is not myotonic. One brother was born dead. The authors insist on the variations in the pathologic picture, especially the anomalies of the electrocardiogram. BAILEY, Chicago [ARCH. NEUROL. & PSYCHIAT.].

Diseases of the Eye

EXTREME PREMATURITY AND FIBROBLASTIC OVERGROWTH OF PERSISTENT VASCULAR SHEATH BEHIND EACH CRYSTALLINE LENS: I. PRELIMINARY REPORT. T. L. TERRY, Am. J. Ophth. **25**:203 (Feb.) 1942.

In a 6 month old infant who was one of twins born prematurely, a grayish white opaque membrane with a serrated edge was found behind each crystalline lens. The pupillary responses were normal; a jerky, irregular, somewhat searching nystagmus was present. Four other cases of a similar growth are mentioned, all occurring in premature infants with birth weights of 3 pounds (1,307 Gm.) or less. It is thought that this membrane grows after birth, since it has no exact counterpart in normal fetal development. The cause is obscure, and up to the present time no successful treatment has been worked out.

LESLIE, Evanston, Ill.

POPULAR MISCONCEPTIONS IN CONNECTION WITH THE EYES. H. M. TRAQUAIR, Edinburgh M. J. **49**:179 (March) 1942.

The author states that misunderstandings, unwarranted assumptions and old-fashioned ideas concerning the eyes are common and cause a great deal of unnecessary anxiety. He makes a few references to childhood and disagrees with the popular warning given children and young people not to hold a book close to the eyes. Since a child tends to find its interest in the immediate surroundings, there is naturally an addiction to books. Short-sighted children especially have an interest in reading for this cause. Therefore, holding the book close to the eyes is an accompaniment and result of the short sight and not the cause of it. Furthermore, many children hold the book close to the eyes because of an intellectual and not a visual difficulty. They may see clearly but find difficulty in comprehending what they read, probably having the idea that they will better understand the meaning if the printed page is held closer. The author states that the tendency to hold the book close to the eyes gradually gets less as brain power develops. Reading in bed does not harm the eyes but may keep the child awake and deprive him of necessary sleep.

NEFF, Kansas City, Mo.

TUBERCULOSIS OF THE CONJUNCTIVA. N. BLUMENFELD, Vestnik oftal. **18**:203, 1941.

Three patients with tuberculosis of the conjunctiva have been seen since 1935 in the ophthalmic clinic of the Crimean Medical Institute. They were 10 years, 2 years and 19 months old, respectively. In 2 the process in the conjunctiva was primary, while in the third it was secondary to tuberculosis of the lungs. The inoculation of guinea pigs intraperitoneally and into the anterior chamber gave a positive reaction in all cases. Ulceration of the conjunctiva of the upper lid with papillomatous granulation and swelling of the preauricular and submaxillary glands was present in all cases. The histopathologic examination showed a tuberculous ulcer with a caseous necrotic center and with epithelioid and giant cells. Surgical removal of the ulcer with cauterization of the wound was followed by cicatrization. Tuberculin therapy and general hygienic measures were also employed.

O. SITCHEVSKA. [ARCH. OPHTH.]

PARINAUD'S SYNDROME AND TUBERCULOSIS OF THE CONJUNCTIVA. N. OCHAPOWSKAYA, Vestnik oftal. **18**:278, 1941.

Ochapowskaya discusses the etiology and clinical picture of Parinaud's syndrome and reports a case in which Parinaud's conjunctivitis proved to be true tuberculosis of the conjunctiva.

A girl aged 15 had a swelling of the left upper lid and of the left preauricular gland for six months. It was diagnosd by a competent ophthalmologist as Parinaud's conjunctivitis. The conjunctiva of the upper lid was infiltrated, and there were vegetations of various sizes, with ulceration. The left preauricular gland was swollen and had two fistulas. Bacteriologic examination of the conjunctival secretion gave negative results. A biopsy of the conjunctiva showed under the microscope typical giant cells, lymphoid cells and epithelioid cells with moderate necrosis.

A second patient was a woman 20 years old in whom the conjunctiva of the right eye was affected and the clinical picture was characteristic of tuberculosis. Since the microscopic examination did not show any giant or epithelioid cells, a diagnosis of Parinaud's conjunctivitis of undetermined causation was made.

The conclusions were as follows:

1. Parinaud's conjunctivitis represents a reaction of the conjunctiva grossly homogenous to but microscopically different from the reaction to various etiologic, frequently undetermined, factors.

2. The further study of Parinaud's syndrome produced more confusion. Ochapowskaya believes that (*a*) Parinaud's conjunctivitis is not an independent nosologic unit and that (*b*) Parinaud's syndrome can imitate grossly various infections such as tuberculosis, syphilis, tularemia and sporotrichosis.

3. Each case should be individually studied from the etiologic point of view in order that a refinement of the prognosis and the therapy may be achieved.

O. SITCHEVSKA. [ARCH. OPHTH.]

Skin Diseases; Allergy

HEREDITARY XANTHOMATOSIS: FAMILIAL INCIDENCE OF XANTHOMA TUBEROSUM ASSOCIATED WITH HYPERCHOLESTEREMIA AND CARDIOVASCULAR INVOLVEMENT, WITH REPORT OF SEVERAL CASES OF SUDDEN DEATH. DAVID BLOOM, SAMUEL R. KAUFMAN and RUSSEL A. STEVENS, Arch. Dermat. & Syph. **45**:1 (Jan.) 1942.

Familial incidence of xanthoma tuberosum has been observed in a Syrian family which in addition to the unaffected but consanguineous parents and 4 unclassified infants consists of 9 children and 8 half-siblings of the mother. Of the 5 children in whom xanthoma tuberosum developed before the age of 4 years, all were affected by a generalized disturbance of the lipid metabolism (hypercholesteremia), and 4 died suddenly between the ages of 6 and 23 years, the cause of death being attributable to xanthomatous lesions in the cardiovascular system.

The authors point out that careful genetic studies of families affected either by xanthoma tuberosum or by hypercholesteremia are essential for the development of successful measures of therapy and prevention.

They believe that a cholesterol-free and fat-free diet may be helpful in protecting hypercholesteremic trait carriers against the development of cutaneous and cardiovascular lesions.

JACKSON, Iowa City.

POISON IVY DERMATITIS: I. THE DIAGNOSTIC VALUE OF THE PATCH TEST MADE WITH AN ETHER EXTRACT FROM FRESH LEAVES AND STEMS OF THE POISON IVY PLANT. EDMUND L. KEENEY, STEWART SUNDAY, LESLIE N. GAY and K. LYNCH, Bull. Johns Hopkins Hosp. **69**:482 (Nov.) 1941.

It is concluded that patch tests performed with a 1:25 peanut oil dilution of an ether extract of the fresh leaves and the stems of the poison ivy plant accurately reveal hypersensitivity in man to the poison ivy plant. The chances of eliciting false positive reactions with this extract are slight.

AUTHORS' SUMMARY.

MULTIPLE SERUM ALLERGY IN ATOPIC INDIVIDUALS. A. IRWIN KLEINMAN and HARRY MARKOW, J. Lab. & Clin. Med. **27**:187 (Nov.) 1941.

Using horse, goat, sheep and rabbit serums, the authors tested 40 atopic persons for multiple serum allergy. Of these persons 12.5 per cent exhibited positive reactions to one or more serums, 10 per cent to two or more serums and 7.5 per cent to all four serums. Every subject with a 4 plus cutaneous reaction gave a positive reaction to a conjunctival test. It was also

noted that sensitivity to animal dander is coincident in many subjects with a sensitivity to the corresponding serum. Extreme care should always be exercised in use of therapeutic serums in allergic patients, no matter which animal serum is used. GARD, Galveston, Texas.

CUTANEOUS DISEASES IN INFANTS AND CHILDREN. THEODORE CORNBLEET, M. Clin. North America **26**:163 (Jan.) 1942.

A selected group of cutaneous diseases frequently encountered in early life is discussed in this paper.

Lichen Urticarius.—This condition, also known as papular urticaria, appears as discrete hard conic papules of flesh color, pinkish to reddish, often puffy at the base. The extensor surfaces of the extremities, the sacral region and buttocks, the shoulders and the face are commonly involved; the trunk, to a lesser degree. The course is chronic, extending over a number of years and cyclic, exacerbating or recurring in the summer. A single lesion lasts about three weeks from onset to subsidence. Itching is intense. Many theories have been advanced as to its cause, but none have been proved. It is a stubborn disease, and treatment has not yielded spectacular results. Solution of potassium arsenite U. S. P. and calcium seem indicated for internal medication, and injections of liver extract and dietary supplements of the vitamin B complex appear to benefit some patients. Locally, colloidal baths of starch and soda give some relief. Lotions are usually better than ointments. In time most subjects are freed of their eruptions.

Impetigo Contagiosa.—Isolation should be practiced in treatment. Ammoniated mercury has stood the test of time and remains an effective remedy. The dyes are valuable, in dispensary practice especially; the best of these is gentian violet in 2 per cent aqueous solution. Sulfathiazole used in 5 to 10 per cent strength in a vanishing cream or surgical lubricating jelly may eradicate the eruption in three to ten days when properly used. Suberythema doses of ultraviolet rays are valuable in preventing the spread of the disease.

Perlèche.—This belongs to the group of disorders due to infection with yeasts. It persistently involves the lip commissures but may extend to the midline of the lips. Early the epidermis appears sodden and parboiled. The surface is smooth and may later crack, exposing a red base. The disease should be differentiated from mucous patches and eczema. A prerequisite for cure is to keep the parts dry. Licking of the lips should be discouraged. The most effective local application is gentian violet in a 1 or 2 per cent aqueous solution. Gram's iodine solution is also of value, especially when used after the local application of gentian violet. Riboflavin is of no value in the treatment of ordinary perlèche; but when the condition is due to malnutrition it is specific. EUGENE SMITH, Ogden, Utah.

EFFECTS OF ROENTGEN IRRADIATION UPON LINEAR RATE OF FLOW IN CUTANEOUS LYMPHATICS OF HUMANS. J. N. ANÉ and GEORGE E. BURCH, Proc. Soc. Exper. Biol. & Med. **48**:471 (Nov.) 1941.

By use of the colloidal dye method of McMaster (*J. Exper. Med.* **65**:347, 1937) to study the lymphatic circulation in 7 adult subjects it was found that small doses of roentgen rays (220 to 450 r) caused no disturbance in the linear flow of lymph in the cutaneous circulation, whereas large doses, sufficient to produce a first degree cutaneous reaction, seemed to cause decrease in the flow of lymph. HANSEN, Minneapolis.

SULPHATHIAZOLE OINTMENT IN THE TREATMENT OF IMPETIGO. ALEX J. STEIGMAN, Brit. M. J. **1**:12 (Jan. 3) 1942.

In this article the author points out the various problems of treating impetigo and states that the success of local therapy depends on two conditions: (1) the contact between the drug and the infectious agent and (2) the bactericidal potency of the drug employed. He also states that at the present time the drugs of choice for the treatment of impetigo are mercurials, organic dyes and sulfonamide compounds.

Bacteriologic examination of 25 patients suffering from impetigo revealed that from nearly 50 per cent of the patients hemolytic streptococci could be isolated in pure culture. From about 32 per cent of the patients Staphylococcus aureus could be isolated in pure culture, and from the rest of them could be obtained a combination of the two organisms. Fifty-one patients with impetigo were treated all together. In 20 of these patients there was generalized impetigo, and the treatment consisted of a good scrubbing in a warm tub and removal of the scabs. On half of the body ammoniated mercury was used three times a day, and on the other half of the body 5 per cent sulfathiazole ointment was used three times daily. The result in this study was most illuminating. After the second day of treatment it was always easy to state which of the preparations had been used on each side of the body. The impetigo

treated with ammoniated mercury healed rather slowly though steadily, about eight days as an average being required. The lesions treated with sulfathiazole ointment showed improvement within forty-eight hours and were healed by the fourth or fifth day. The lesions of the remaining 31 patients were treated entirely with sulfathiazole ointment without any attempt of comparison. The results were identical with those obtained on that side of the body which had been treated with sulfathiazole in the first group. It was noted that impetigo of the hairy scalp was more resistant and usually required an average of eight days for healing. It is recommended by the authors that impetigo and underlying scabies infection be treated first with sulfathiazole ointment and then with the application of sarcopticides. By treating the condition in this way effective results can be obtained with much less discomfort.

ROYSTER, University, Va.

A CASE OF CONGENITAL ICHTHYOID ERYTHRODERMIA. JORGE MILLAN GUITIERREZ, Rev. mex. de pediat. **11**:449 (Dec. 10) 1941.

Guitierrez presents the case of a girl 11 years old. She was slow in developing and did not talk until she was 3 years old. She had colic pain in the abdomen and yellow stools at times, with blood and a fetid odor. She also had photophobia.

At the time of examination she was 1.28 meters tall and weighed 23 Kg.

Examination showed a girl with a generalized dermatitis, mostly on the head, on the upper and lower extremities and in the pubic region.

Morphologically the lesions were of three types: erythrodermic, hyperkeratotic and pseudopapillomatous.

She was treated with pentavalent arsenic and bismuth. There was some improvement in the lesions of the head and those of the pubic region.

She was also given anterior pituitary substance to increase her growth and all the vitamins.

GIFFEN, Toledo, Ohio.

Teeth and Dentistry

ORTHODONTICS AND GROWING UP. CLIFFORD SWEET, Am. J. Orthodontics **27**:546 (Oct.) 1941.

Any child who has an orthodontic deformity generally has a deformity that extends throughout his whole body. The author believes body mechanics is important and discusses it from infancy on through to adulthood.

LEWIS, Dayton [ANGLE ORTHODONTIST].

STUDIES IN TOOTH DEVELOPMENT: THEORIES OF ERUPTION. MAURY MASSLER AND I. SCHOUR, Am. J. Orthodontics **27**:552 (Oct.) 1941.

The purpose of this paper was to test the validity of the various theories of eruption by the results of clinical and experimental findings; to integrate the facts which seem plausible, and to suggest further experimental studies on the eruption problem. The search revealed considerable circumstantial and a small amount of factual evidence against all theories except one. There is considerable circumstantial evidence but no actual proof in favor of the theory that vascularity of the peridontal tissues is an important factor in the causation of eruption. Clinical and experimental evidence shows that the eruptive force is probably located in the periapical region of the tooth. Experiments for controlling the vascularity of the tissues are suggested.

LEWIS, Dayton [ANGLE ORTHODONTIST].

BEHAVIOR OF NORMAL AND ABNORMAL FACIAL GROWTH PATTERNS. ALLAN G. BRODIE, Am. J. Orthodontics **27**:633 (Nov.) 1941.

This presentation deals with the morphogenetic and appositional phases of normal and abnormal growth processes. On the morphogenetic pattern appositional growth takes place and can be expressed by locus, rate, age and time gradients. The principles and gradients concerning teeth are discussed and are shown to hold true also for skeletal growth.

Normal growth of the cranium and head is steady, not changed in form, and proportionality is maintained because all anatomic points travel on straight lines. Several types of abnormal growth are illustrated; such deformities, except those caused by accidents or surgical measures, show neither improvement nor regression as the person gets older. These deformities are caused by adverse factors operating at the time certain growth centers are active.

LEWIS, Dayton [ANGLE ORTHODONTIST].

DENTAL FLUOROSIS AND CARIES IN LONDON CHILDREN. MARGARET M. MURRAY and DAGMAR C. WILSON, Lancet **1**:98 (Jan. 24) 1942.

In America, Dean and his colleagues proved that in certain groups of children there was a relative immunity to dental caries associated with the intake of natural waters containing

fluorine up to 1.8 parts per million. In England, Wilson correlated in a general way the occurrence of fluorosis, as indicated by mottling of teeth, with soils likely to contain fluorine and also the occurrence of mottling and dental caries. She proved that a greater immunity to caries is associated with fluorosis.

Five hundred and eighty-nine children resident in 99 London districts were investigated for mottled enamel and dental caries. The figures obtained show that, including all the grades of fluorosis but excluding the questionable, 28 per cent of the 589 children between the ages of 10 and 15 years had some mottled teeth, and the previously reported negative association of fluorosis and caries was again borne out. Samples of the three main sources of London's water supply were analyzed and the fluorine content found to be low as compared with contents reported from other countries.

LANGMANN, New York.

Miscellaneous

SOME EFFECTS OF SULFANILAMIDE ON MAN AT REST AND DURING EXERCISE. F. J. W. ROUGHTON, D. B. DILL, R. C. DARLING, ASHTON GRAYBILL, C. A. KNEHO and J. H. TALBOTT, Am. J. Physiol. **135**:77 (Dec.) 1941.

During rest and during moderate exercise (metabolic rate 5 to 6 times that at rest) the rate of carbon dioxide elimination is unchanged in human subjects by administration of sulfanilamide to a blood concentration of 3 to 4 mg. per hundred cubic centimeters.

In exhausting exercise there is definitely some handicap in removal, resulting in the damming back of carbon dioxide. This adds to the acidosis of lactate formation and results in prolonged dyspnea during recovery.

The degree of psychologic and general physical handicap observed in subjects taking 2 to 3 Gm. of sulfanilamide daily was severe enough to make its prophylactic and therapeutic use unsuitable for patients expected to continue exacting or strenuous work, especially if this requires skill.

NOURSE, Cleveland.

IMMUNITY RESPONSE TO NONSPECIFIC ANTIGENS. H. GHOSH, J. Indian M. A. **11**:100 (Jan.) 1942.

The authors determined the leukocyte response in normal adults to protein antigens commonly used in India (milk protein, typhoid-paratyphoid vaccine, protozoal vaccine and albulipins. With none of the antigens did the duration of the negative phase last for more than two hours, being least marked with milk. The maximum leukocyte response to all antigens appeared within twelve to twenty-four hours. Leukocytosis after primary stimulation was greatest with milk, and next in order came protozoal vaccine, albulipin and bacterial protein. After repeated injections on alternate days the greatest leukocytic response occurred with albulipins. Constitutional reactions were most severe with typhoid-paratyphoid vaccine and least with albulipin and protozoal vaccine.

GONCE JR., Madison, Wis.

THE STRANGE DURBAN EPIDEMIC OF 1937. B. F. SAMPSON, South African M. J. **16**:2 (Jan. 10) 1942.

Evidence is presented to prove that an epidemic of peripheral neuritis of the bilaterally symmetric motor type, in which there was a predilection for the muscles below the knees and the intrinsic muscles of the hands, was due to poisoning by triorthocresyl phosphate. This chemical was recovered from a cooking oil that had been used at all of the main foci of the epidemic. Feeding of the oil to cockerels was followed by weakness and incoordination of the legs and, eventually, inability to stand. Histologic examinations of the spinal cords of these fowls showed capillary engorgement, migration of round cells into the gray matter and chromatolysis and vacuolation of anterior horn cells of the lumbar enlargement. The drums in which the oil had been shipped (from London) differed somewhat in size and pattern, which suggested they had been used previously for some other purpose. A drum of commercial tricresyl phosphate, known to the trade as "Lyndol" or "lindol," might have been used by a firm in England for rendering paint or varnish plastic for the manufacture of cellophane or photographic film and then sold as an "empty" to the firm exporting the oil to South Africa. Clinically, the disease was similar to "ginger" or "jake" paralysis, which occurred in epidemic form in the United States in 1930, and to apiol paralysis, which occurred among many European women in 1932. In both of these epidemics the causative agent was triorthocresyl phosphate. The disease had to be differentiated from toxic polyneuritis due to infection or other exogenous toxins, from Guillain-Barré disease and from woodtick paralysis.

GONCE JR., Madison, Wis.

Society Transactions

CHICAGO PEDIATRIC SOCIETY

JESSE R. GERSTLEY, M.D., *President*

Feb. 16, 1943

Two Cases of Pressure Pneumothorax. ROWINE HAYES, M.D.

The first patient, an infant aged 5 months, was admitted to the hospital on Jan. 5, 1943. One day prior to admission she suddenly became ill, and fever (temperature 104.6 F.) and rapid labored respiration developed. The chest showed dulness over the entire lower lobe of the left lung anteriorly and posteriorly and moist rales over the entire lower lobe of the left lung; apparently fluid was not present. Within twelve hours the conditions in the chest changed. There was complete dulness over the left side, with flatness over the entire lower lobe of the lung and shift of the mediastinum to the right. Roentgen examination confirmed the presence of empyema, and by aspiration 25 cc. of purulent material was evacuated, which on culture yielded hemolytic staphylococci (Staphylococcus aureus).

Closed drainage was instituted. The tube was put in the left side of the thoracic cavity, and a large amount of purulent material was drained off. About six hours later the child began to blow bubbles through the tube; a pneumothorax had developed. She has been treated with sulfapyradine. The tube is still in the chest cavity, and there is still a small amount of drainage, but the bronchopleural fistula has closed.

The second patient, a 2½ month old baby, was admitted to the hospital on January 20, with a history that was normal until about a week prior to admission when a mild infection of the upper respiratory tract developed, with a small amount of nasal discharge and cough. The night before admission she suddenly had rapid labored respiration and spells of cyanosis. When brought in she was acutely ill and cyanotic, with mottling of the skin of the entire body and labored respiration. There were hyperresonance of the left side of the chest and exaggerated breath sounds, a dull percussion note on the right side and practically no air moving in on the right side; there were a few rales. The mediastinal structures were displaced into the left side of the thoracic cavity. The apex beat was palpable about ½ inch (1.3 cm.) to the left of the left nipple. As there was no air moving in the right side of the chest, it was thought to be atelectasis; but the mediastinum was pushed to the left, and it was felt that air was present in the right pleural cavity under pressure. The child appeared to be dying.

On the assumption that she had pneumothorax, the right side of the chest was aspirated and air was obtained under pressure, after which she was better for a few moments; then the severe toxemia and cyanosis returned. It was felt that adequate drainage should be established so that the tension pneumothorax could be relieved. Close drainage was instituted; the tube was connected to a water bottle, and for eighteen hours bubbles came out through the tube each time the patient breathed. She was kept under oxygen for several days, and the tube remained in place for nine days. She looks well now and has no trouble in breathing. There is still not so much air going into the right side of the chest as there should be, but her recovery has been satisfactory to date.

There are three or four possibilities to be considered in the diagnosis. It is known that she had a pressure pneumothorax after aspiration, but whether it was present before that is not known. There may have been an emphysematous bleb in the right lung. One would have to assume it to be extremely large to collapse the middle and lower lobes. It may be that if such a bleb was present it was ruptured when the needle was inserted. Another possibility is a pulmonary cyst, which is rare in children of this age. From the roentgenograms a diagnosis of cyst in the middle lobe of the right lung might be made, inasmuch as this lobe did not show up well on the films. If such a cyst were ruptured, it is not clear why the local treatment should affect the check valve mechanism that should be present in the bronchus. A fourth possibility is obstructive emphysema; here also the pathologic changes would have to be in the middle lobe of the right lung. Whatever the diagnosis, it is certain

that she had pneumothorax at some time and if it had not been successfully interfered with she would probably have died. Bronchoscopy will be performed at a later time to ascertain the condition of the lobe.

Presentation of a Case of Heart Disease. STANLEY GIBSON, M.D.

This boy will be 6 years old this week. His present weight is 25 pounds (11.3 Kg.). He was born about four weeks prematurely, and his birth weight was 3 pounds 12 ounces (1,700 Gm.). He has never gained well. He was brought to the hospital at the age of 10 months because of malnutrition. Physical examination at this time showed a continuous loud murmur at the base of the heart characteristic of patent ductus arteriosus. He came back to the hospital a number of times because of infections of the upper respiratory tract. In October 1942 he entered the hospital with symptoms and signs of pneumonia. Use of sulfathiazole was instituted, and the temperature subsided within four days.

At this time there was one physical symptom which was disturbing: The spleen was considerably enlarged. A culture of the blood yielded Streptococcus viridans. Since then the boy has received various sulfonamide compounds, sulfadiazine being best tolerated and most effective in controlling the fever. Recent cultures of the blood have not yielded streptococci.

This patient presents three interesting features. In the first place, the full-blown humming top murmur of patent ductus arteriosus was found at the age of 10 months. This murmur is usually of slow evolution, and this is the only instance in which I have encountered it in the first year of life. In the second place, the handicap of the patent ductus was sufficiently severe to interfere seriously with normal gain in weight. The third interesting point is the fact that his symptoms of bacterial endarteritis have responded well to large doses of sulfadiazine, although I am not optimistic as to the prospect of a permanent cure.

Chronic Intussusception. E. T. MCENERY, M.D.

Intussusception in children is not an unusual condition. In a brief review of the literature, it was found that Ladd and Gross, of Boston, have reported the largest series, 484 patients in a period from 1908 to 1939, with an average of 20 per year. In 5 of these the condition was chronic. In 17 the intussusception was associated with Meckel's diverticulum; in none of the patients with chronic intussusception was this a possible etiologic factor. In Children's Memorial Hospital during a six year period 50 cases have been recorded, none of a chronic nature; in only 2 was the anomaly associated with Meckel's diverticulum.

This white boy aged 16 months had been well until October 1942, at which time he started to vomit and had some abdominal pain. He passed a formed stool and during the day passed more stools which contained a large amount of bright red blood. On the following morning, when I examined him, there was no elevation of temperature, the abdomen was soft and I was unable to palpate any definite point of tenderness or any masses. Rectal examination revealed a large amount of old blood. A flat plate roentgenogram of the abdomen was taken but showed nothing significant. The acute symptoms subsided, but the blood streaking of the stools persisted. Proctoscopic examination showed no pathologic changes in the rectum. During one month's stay in the hospital the abdomen was examined frequently, and on several occasions it was thought that a mass was felt to the left of the midline. The stools were constipated; when a large enema was given, this mass seemed to disappear. Because of persistent blood in the stools, the diagnosis of Meckel's diverticulum was made and an exploratory operation was advised; the parents refused.

In the early part of January another spell of acute abdominal pain occurred, associated with vomiting and a large amount of blood in the stool. A barium sulfate enema was given, and the conditions characteristic of an intussusception were shown by roentgenogram. The patient's general condition was good. He was having a stool daily, occasionally streaked with blood. At this time a large mass could be palpated to the left of the midline. On Jan. 8, 1943, he was operated on by Dr. Montgomery, who found a chronic intussusception about 10 inches (25 cm.) long about 12 inches (30 cm.) from the iliocecal valve. The intussusception was covered with yellow fibrinous exudate. The mesenteric glands were large and firm. The mass was difficult to reduce, although various means, such as application of hot laparotomy pads and an injection of glycerin, were tried. During the manipulation the bowel was ruptured, and a large Meckel diverticulum presented. This was about 6 inches (15 cm.) in length, hard and edematous, with gangrene at the base. This was removed. Because of the condition of the bowel a small portion had to be resected, and an end to end anastomosis was performed. The postoperative course was not stormy. Nothing was given

by mouth for nine days. Fluids, citrated blood, dextrose, Ringer's solution and lactate-Ringer solution were given by vein. The boy remained in the hospital for two and a half weeks. The only complication was a superficial abscess in the wound.

This case is unusual because of the length of time that the intussusception was present, possibly two and a half months. The obstruction was not complete, as the patient had a daily bowel movement. The remarkable point is that he showed so little toxemia, even though the intussusception was extensive and the bowel gangrenous.

Subpectoral Abscess. HERMAN F. MEYER, M.D.

This patient, 7½ years old, was seen also by Dr. Aldrich and Dr. Montgomery in consultation during his stay in the hospital. Other than scarlet fever two years ago there was nothing unusual in the medical history. The boy was first seen with severe pain in the left side of the chest, radiating down the right arm. The pain was intense and constant, and large doses of codeine were required for its control. There was no history of local trauma or recent infection. He was restless and toxic. Two days later the temperature was 101 F. and there was slight swelling from the left axillary line to the nipple. After administration of sulfathiazole for three days he became afebrile, but the tenderness persisted. A tentative diagnosis of osteomyelitis of the ribs was made.

After three more days an abscess was localized in the left subpectoral region, and after incision and drainage culture of the pus yielded hemolytic staphylococci (Staphylococcus aureus). The flatness over the upper part of the chest indicated the presence of fluid, and this was confirmed by roentgen examination. A forceps was passed through the original incision, and about 200 cc. of clear fluid was obtained. The fever subsided, and complete recovery ensued after five weeks.

This is an unusual site for an abscess. There is no report of any subpectoral abscess in the records of Children's Memorial Hospital. There are 11 cases reported in the literature in which a subpectoral abscess was associated with trauma or a foreign body. This report deals with an abscess in the subpectoral region without known cause.

Autopsy Report of a Case of Neuroblastoma. MARK F. CANMANN, M.D.

J. C., a 19 month old white girl, was a full term, spontaneously delivered baby weighing 9 pounds (4,082 Gm.) at birth. Four months prior to her admission to Children's Memorial Hospital she weighed 30 pounds (13,608 Gm.). At that time her mother said she became less active and somewhat listless and lost her appetite. One month before admission the mother noted that the abdomen was enlarged, that the child was pale and that she was losing weight. She had had a low grade fever for several months, and recently a cough had developed. The urine and stools were normal.

On examination, she appeared chronically ill, listless and irritable, though rather well developed. The skin was pale and warm. Dulness and distant breath sounds were found over the lower lobe of the left lung. The abdomen extended 1 inch (2.5 cm.) above the chest level; a large firm, smooth mass, extending from the costal margin to the pelvis on the left side just to the right of the midline, was palpated. A second mass, small and movable, measuring approximately 6 by 3 cm., was felt superimposed on the large tumor. Beneath the xiphoid process a third mass was felt; it was not movable and apparently was not connected to the larger mass. There were no palpable lymph nodes. The urogram showed some portions of the pelvis to be on the left.

Examination of the blood showed a hemoglobin content of 6 Gm., 2,000,000 red cells and 14,000 white cells, with 40 per cent polymorphonuclear leukocytes, 58 per cent lymphocytes and 2 per cent monocytes. The urine was normal. Determination of the blood chemistry showed 28 mg. of nonprotein nitrogen and 1.5 mg. of creatinine per hundred cubic centimeters. A tuberculin test gave a negative reaction. Roentgenograms showed a soft tissue shadow, somewhat oval in outline, in the upper half of the left pulmonary field. The leaves of the diaphragm occupied high positions, tipping the heart on its side. After intravenous injection of diodrast the soft tumor mass was seen in the upper left quadrant extending almost to the crest of the ileum. No evidence of dye was seen in the mass, but dye was seen in the pelvis and calices of the kidney below the mass; the right kidney was in normal position. The roentgenogram of the bones revealed a destroying process involving the proximal third of the shaft of the right humerus and the left femur just proximal to the distal epiphysial line. The skull appeared normal.

During the eight days she remained in the hospital the child's temperature varied from 99 to 101 F. She was listless and lay quiet in bed until death occurred, on the ninth day.

At autopsy this 19 month old girl weighed 22 pounds (9,980 Gm.) and was 34 inches (86.4 cm.) long. A large mass was found in the abdomen, extending from the left costal margin to the level of the anterior superior iliac spines, 1.5 inches (3.8 cm.) to the right of the midline. The second mass, superimposed on the large tumor, proved to be the spleen. Enlarged lymph nodes were found in the right and in the left inguinal regions, in the right axilla and in all the triangles of the neck. The tumor mass measured 7 by 6 by 4 inches (17.8 by 15.2 by 10.2 cm.) and extended from the ribs to the ilium. At the inferior lateral aspect was embedded the left kidney, which was one and one-half times as large as the right. The right kidney showed a metastatic lesion in the cortex. The right adrenal gland was normal, but no tissue of the left adrenal gland could be recognized. The mass was adherent to the left leaf of the diaphragm, had eroded through it and was continuous with a similar mass found in the base of the left side of the chest. The left lung was completely collapsed; metastatic lesions were found in the upper and lower lobes. Metastatic lesions involved the right femur and humerus, the fifth and eighth ribs on the right and the second, eighth, ninth and tenth ribs on the left. Two areas of metastasis were found over the right parietal and the right frontal bone. All the lesions were brownish red and exuded a thick bloody fluid. Other metastatic lesions included the hilar and peritoneal lymph glands.

On microscopic examination the characteristic cells were small, round to slightly oval and for the most part in clumps; in two slides the tumor cells were arranged in rosettes. There were much hemorrhage and necrotic tissue in the cysts.

The following cases were also presented:

Surgical Treatment of Cerebral Spastic Paralysis. FREMONT A. CHANDLER, M.D.

A Case for Diagnosis. DOUGLAS BUCHANAN, M.D.

Foreign Bodies in Air and Food Passages. PAUL H. HOLINGER, M.D.

News and Comment

GENERAL NEWS

Dr. Helmholz Honored.—Dr. Henry F. Helmholz, chief of the pediatric service of the Mayo Clinic, Rochester, Minn., was awarded the honorary degree of Doctor of Science at the University of Wisconsin, May 29, 1943.

Book Reviews

Infant and Child in the Culture of Today. By Drs. Arnold Gesell and Francis L. Ilg, in collaboration with Janet Learned, M.A., and Louise B. Ames, Ph.D. Price, $4.00. Pp. 399, with 17 illustrations. New York: Harper & Brothers, 1943.

This is the nineteenth volume which has been contributed by Dr. Arnold Gesell with the aid of his associates. The latest volume is similar to the first, "The Normal Child and Primary Education," in title but is strikingly different in content. The difference lies in the addition to this volume of the results of many years of research which Gesell and his associates have carried out at the Yale Clinic and the advances in the whole field of child psychology.

In previous volumes Gesell has dealt mostly with growth and development. This volume devotes more space to the problem of management of children up to 6 years of age.

The first part of the book deals with the general concepts of growth, emphasis being placed on the development of the nervous system and the picture of the world as experienced by the child. "The child develops as a whole. Emotions grow and mature in the same sense that perceptions, judgments and concepts grow and mature. . . . Infants are individuals. They are individuals from the moment of birth. Indeed, many of their individual characteristics are laid down long before birth." Throughout these chapters the authors emphasize the importance of allowing the innate potentialities of the individual child to develop rather than forcing cultural patterns on the child.

Part two, considered by the authors as the main part of the book, is an objective description of the characteristics of mental growth during the first five years of life. Twelve behavior profiles are described in detail. This material is similar to that given in previous volumes, but more interesting details are presented.

Part three takes up the "Guidance of Growth." Here the general concepts of discipline are discussed, the authors again emphasizing the developmental point of view. Problems of sleep, feeding, bowel control, sex interest, socialization and guidance are discussed. The last includes nursery school technics. The appendixes discuss briefly nursery school equipment, toys and play materials, reading material and musical records.

It is obvious, therefore, that in this volume the authors have given an overall description of child care. This approach has necessitated a collaboration of the physician, the psychologist and the nursery school educator. Naturally, these viewpoints have not been put together in a manner that does not bring up questions and even objections to some minor details of management. As a whole, however, it will be generally agreed that this is an outstanding major contribution to the study of child care and should be a text for every one—parent, teacher and physician alike.

Correspondence

ADDITIONAL REPORT ON PREMENSTRUAL STATE IN YOUNG GIRLS

To the Editor:—In the February 1943 issue of the AMERICAN JOURNAL OF DISEASES OF CHILDREN in the article "Premenstrual State in Young Girls" it was stated on page 304 that no report of studies on the vaginal reaction had been found in the literature. My attention has been called to the excellent article by Gertrud Soeken, "Beitrag zur Physiolgie der Pubertät: Der Umschlag der chemischen Reaktion im Vaginalsekret" (*Ztschr. f. Kinderh.* **47**:27, 1929). Mr. Tuchewicz and I regret this oversight.

J. D. PILCHER, M.D., Cleveland.

3395 Scranton Road.

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